febrile seizures
clinical and genetic studies

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Proefschrift

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To all children with febrile seizures and their parents

Voor Jip

Contents

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Introduction

1.1 Clinical and genetic aspects

Clinical aspects

Febrile seizures are described as a temporary seizure disorder of childhood; the attacks occur by definition in association with fever and are usually accompanied by sudden tonic-clonic muscle contractions and reduced consciousness, usually lasting not longer than 5 to 10 minutes. According to the commonly accepted definition of the National Institutes of Health consensus meeting of febrile seizures in 1980, 'a febrile seizure (an abnormal, sudden, excessive electrical discharge of neurons [grey matter] which propagates down the neuronal processes [white matter] to affect an end organ in a clinically measurable fashion) is an event in infancy or childhood, usually occurring between three months and five 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. Febrile seizures are to be distinguished from epilepsy, which is characterised by recurrent nonfebrile seizures'.[1] In the context of this thesis, fever has been defined as a rectally measured body temperature of 38.5 °C or higher. Complex febrile seizures have one or more of the following characteristics: the seizure lasts for more than 15 minutes (prolonged) or 30 minutes or more (febrile status epilepticus); there are one or more recurrences within 24 hours (multiple type febrile seizures); the seizure has partial features, i.e. a focal onset of the seizure or a postictal Todd paresis of facial muscles or limbs.[2-4] Seizures are referred to as simple, if they last less than 15 minutes, do not recur within 24 hours (single-type) and are generalised.

Several studies have described the clinical presentation of febrile seizures.[4-11] Males are more frequently affected than females; ratios vary between 1.1 and 1.6. Half of the children have their initial seizure at 16-18 months of age. On average 65 to 80% of all children with febrile seizures suffer from a simple initial febrile seizure. If initial and recurrent seizures are considered, 60 to 67% of the children experience simple febrile seizures only. About half of the seizures are of two minutes' duration or less. Only 4 to 14% of the children have an initial febrile seizure lasting longer than 15 minutes. Of the children with febrile seizures 2 to 6% experience a partial initial seizure, although one large study reported a much higher number of 18%.[5] 9 to 19% suffer from a multiple-type initial seizure; one hospital based study reported a higher frequency of 25%.[11] There is a strong correlation between focality and prolonged seizure duration for both first and recurrent seizures. In children with recurrent febrile seizures, complex characteristics tend to reiterate, especially if the duration is long.[4]

Upper respiratory tract infections, gastro-enteritis and viral exanthem are most often the cause of fever in children with febrile seizures. In about 25% of the patients with an initial febrile seizure, no clinical diagnosis of the cause of the fever is found.[5,12] Conflicting evidence exists about the role of viral infections in febrile seizures. Several studies have found no association between viral infections and the occurrence of febrile seizures. One study described that the aetiology of infections (whether or not of viral origin) between children with a first febrile seizure and matched controls with fever caused by infections does not differ.[13] Accordingly, another study found no evidence for viral infections as the most important cause of fever in initial and recurrent febrile seizures.[12] In this study, however, viral isolations from

cerebrospinal fluid (CSF) were positive, which is contradictory to the definition of febrile seizures excluding children with infections of the central nervous system.[1,14] More evidence has been presented about the role of Human Herpesvirus-6 (HHV-6) infections in febrile seizures. These infections have shown to be frequently associated with initial febrile seizures.[15] In a large study of young febrile children the general frequency of primo infections with HHV-6 was determined at 10%.[16] This study described that of all febrile seizures occurring during the febrile course, 31% was associated with a primary HHV-6 infection. All seizures were initial febrile seizures. In a few CSF samples, also from children with febrile seizures, HHV-6 was detected by Polymerase Chain Reaction (PCR), which may also be considered contradictory to the definition of febrile seizures. Recent primary HHV-6 infection was shown in sera of febrile children; in those with a recent primary HHV-6 infection, 30% experienced a febrile seizure.[17] Suggestions have been made for HHV-6 to invade the brain during the acute phase of exanthem subitum. Recurrence of febrile seizures may be associated with virus reactivation.[18] In children with roseola infantum, however, no increase in seizure recurrence frequency was shown; no laboratory tests were performed to confirm the clinical diagnosis.[6] A recent study, in which the follow-up of children with a first febrile seizure with positive and with negative HHV-6 cultures was compared, confirmed these findings.[19] Although beyond the scope of this thesis, the role of HHV-6 clearly needs to be further looked into to understand the pathogenesis of febrile seizures.

A febrile seizure can only be diagnosed after exclusion of an underlying disease which may cause the seizure. Febrile seizures are to be differentiated from acute symptomatic convulsions, whether or not accompanied by fever, which are caused by intracranial infections (meningitis or encephalitis), trauma capitis, biochemical abnormalities (hyponatremia, hypoglycaemia or hypocalcemia) and intoxication. The major differential diagnosis in children presenting with a seizure associated with fever is bacterial meningitis. The reported overall prevalence of meningitis among children with seizures associated with fever varies between 1.2 and 7%.[20-23] According to the NIH Consensus (1980) and British and American recommendations published more recently a lumbar puncture is only indicated if there is a clinical suspicion of an infection of the central nervous system.[1,24,25] In most cases meningitis can be ruled out on the basis of the clinical information, in which, in addition to the presence or absence of nuchal rigidity and petechiae, complex seizure characteristics play a differentiating role.[23] Lumbar puncture is recommended to be performed in young children because of eventually absent or just subtle clinical meningeal signs and symptoms (< 1 year). Previous treatment with antibiotics or diazepam may mask signs and symptoms of meningitis.

Blood tests, i.e. glucose, calcium and sodium levels, aim to exclude an underlying metabolic disorder, which may have contributed to the seizure but which is not apparent in the patient history and physical examination. In the NIH consensus it has been stated that blood tests are rarely useful in the uncomplicated (simple) febrile seizure.[1] This has been confirmed by more recent guidelines, which state that blood laboratory evaluation is usually not required.[24,25] The guidelines have been based on previous studies in which it has been shown that young age (younger than 12 to 18 months of age), metabolic or gastrointestinal disease and complex seizure characteristics are important differentiating factors.[26-30] The evaluation of combinations of specific history and physical examination characteristics, that might identify the individual child at risk for biochemical blood abnormalities or, inversely, identify those children for whom laboratory tests at presentation are unnecessary has not been addressed in

these studies. A prediction model for the exclusion of biochemical abnormalities as the underlying cause of the seizure may give a hand to decide whether or not metabolic blood tests are indicated in the individual patient with a febrile seizure: study aim 1, chapter 1.2.

In children presenting with febrile seizures measurement of erythrocyte sedimentation rate, C-reactive protein level, peripheral leukocyte count and leukocyte differentiation are often performed to evaluate the source of the fever.[24] In clinical pediatric practice it is suggested that leukocytosis might be explained by the seizure duration itself rather than by the cause of the infection. The hypothesis is that increased leukocytes counts in febrile seizures are due to stress-induced redistribution of leukocytes. This concept of seizures changing the peripheral leukocyte count is based on extrapolation of previous findings in animal studies and in studies of human adults.[31-35] On the other hand, these findings have not been confirmed by other investigators who studied primates and human adults: changes in leukocyte counts after prolonged seizures were neither demonstrated in the cerebrospinal fluid nor in the blood.[36,37] We have not found any study providing evidence that febrile seizure duration is associated with an increased leukocyte count. It seems that the diagnostic value of peripheral leukocytosis in children with a long lasting febrile seizures is unclear: study aim 2, chapter 1.2.

Impact of febrile seizures on parents

Most parents who witness their child's febrile seizure are extremely frightened and may even think that their child is dying.[38-40] Although febrile seizures generally are harmless to the child [41-43] they have substantial impact on its family life. Consequences for parents were assessed in a previous study on psychological sequelae of having a child affected by febrile seizures: parental sleeping problems were a predominantly existing problem, worsening with the frequency of the child's seizure recurrences.[39] Despite the fact that these studies have shown the problem of parental fear it is not known whether the current provision of information to parents about fever and febrile seizures has a positive effect on the parents' attitude: study aim 3, chapter 1.2.

Prognosis

The prognosis of febrile seizures relates to three issues: the risk of brain damage, the risk of developing epilepsy later on and the risk of a febrile seizure recurrence.

There has been a historic debate about the connection between febrile status epilepticus and mesial temporal sclerosis.[41,44-46] Based on calculations on the data of a large epilepsy cohort, febrile status epilepticus followed by mesial temporal sclerosis does not occur in more than 1 in 150,000 children,[41,42,47] and the associations found do not prove a causal relation.[45] The evidence provided suggests that, if seizures cause damage, this seldom happens and that this depends on the underlying cause of the seizure which precludes febrile seizures. Hospital-based and retrospective studies show a biased higher frequency of damage after febrile seizures compared to population-based studies which have collected their data prospectively. Prospective long-term follow up studies show that febrile seizures are not associated with

psychomotor developmental delay.[48-50] If all studies are taken into account no clear association is found between febrile status epilepticus and a higher risk of brain injury or impaired intellectual performance.[41,48,51,52] Neither are frequent recurrences of febrile seizures harmful.[42,43]

Epilepsy is defined by recurrent unprovoked (afebrile) seizures, at least two or more.[53] The risk of developing afebrile seizures or epilepsy in children who suffered from febrile seizures is only slightly higher compared to children not affected by febrile seizures. Children not affected by febrile seizures have a risk of developing epilepsy of 0.4 to 0.5%.[54,55] Retrospective studies of children with epilepsy showed that 15% of all children with epilepsy have a previous history of febrile seizures, which is substantially higher than the general prevalence of febrile seizures of 4%.[47,55-57] Prospective follow-up studies of children with febrile seizures demonstrated that children with simple febrile seizures have only a slightly increased risk of developing recurrent afebrile seizures (epilepsy): between 1 and 1.5%.[54,55] If febrile seizures are associated with complex seizure characteristics the risk of developing afebrile seizures or epilepsy later on increases. Febrile seizures cohort studies report probabilities of epilepsy of 6 to 10%.[7,55,58] If focal characteristics are present this risk increases to 8% or higher.[7,58] If two or three complex characteristics are present the risk may rise up to 30 to 40%.[7,55,59] If one or both parents are affected by an epileptic disorder the child has an increased risk of 4% of developing afebrile seizures or epilepsy later on.[7,60] If the child has a family history of epilepsy and has suffered focal febrile seizures the estimated risk is 13%.[7] The number of febrile seizure recurrences do not affect the risk of epilepsy later on which implies that interventions to prevent recurrent seizures early in the course of febrile seizures do not alter the natural course with respect to the risk of developing epilepsy.[41,42]

Until recently children with febrile seizures underwent electroencephalographic tests (EEG), either to diagnose epileptic activity or to assess the risk of febrile seizure recurrence. No evidence exists, however, that an abnormal EEG after the first febrile seizure is predictive for either the risk of febrile seizure recurrence or the development of epilepsy.[24,57,61,62] The EEG may be used as a diagnostic aid only in a few patients suspected of an epileptic disorder or of symptomatic convulsive abnormalities. The family history, the duration and the localisation of the seizure have more prognostic value than the EEG.[25,27] Therefore, the EEG has been abandoned as a prognostic indicator in children with febrile seizures.[1,25]

The risk of febrile seizure recurrences has been studied rather thoroughly.[6-12,63,64] The overall probability of a seizure recurrence is 30% within a 2 years' follow-up with a rapidly decreasing risk after the first six months following the previous seizure. Several risk factors have been determined, of which the major and most consistent are: young age at onset, family history of febrile seizures, previous recurrent febrile seizures, time lapse since previous seizure less than six months, a low body temperature at the first febrile seizure and a multiple-type first febrile seizure. In a meta-analysis of a large data set comprising the pooled data of 2496 individual participants of five febrile seizure cohort studies, including the study that was performed in the Sophia Children's Hospital,[10] risk factors for seizure recurrence were investigated.[64] The results of this study had an important impact on the design of the studies regarding febrile seizure recurrence, as reported in this thesis.

Additional to these risk factors evidence has been put forward that frequent febrile episodes are associated with an increased recurrence risk.[65,66] These studies, however, contain some methodological flaws. One study evaluates retrospectively data on the frequency of fever episodes and seizure recurrences obtained by using a mailed questionnaire. This method may lead to recall bias and overestimation of the effect of fever episodes on seizure recurrence risk. Furthermore, no quantitative results, i.e. odds ratio or relative risk, were reported.[65] In the other study, in which the data were collected prospectively during one year, the frequency of fever episodes was divided into two categories: less than four versus four or more fever episodes per year.[66] The highest risk of a febrile seizure recurrence, however, is within six months after the last previous seizure and the mean number of fever episodes per year in children with febrile seizures may be lower than four.[65,66,78,80] Therefore, assessment of seizure recurrence risk in a six months' follow-up may give a more concise view on the association between the number of fever episodes and febrile seizure recurrence: study aim 5, chapter 1.2.

Furthermore, it is important to be able to predict a recurrent febrile seizure especially at the time the child is again feverish. The body temperature at the onset of the fever and during the fever episode plays an important role in the development of a febrile seizure.[9,67,68] Age is an additional factor influencing the vulnerability of a child to develop a febrile seizure.[64,69] The possibility to predict a febrile seizure recurrence in subsequent fever episodes using temperature and age as the main predictors has not been studied before: study aim 6, chapter 1.2.

Preventive treatment of recurrent febrile seizures

In recent years the prevention of recurrent febrile seizures has become a debatable issue: prevention may not be strictly necessary, because febrile seizures are benign and have a very good prognosis, even for children with long-lasting seizures or frequent recurrences.[41-43] Prevention of febrile seizure recurrences, however, serves two useful purposes: meeting parental fear of recurrent febrile seizures and reducing the, very small, risk of a long lasting and eventually injurious recurrent seizure. One could consider either continuous or intermittent treatment to prevent febrile seizure recurrences. Continuous treatment is to be given every day during at least six months, while intermittent treatment means that medication is used only during fever.

Children with recurrent febrile seizures used to be treated continuously with antiepileptic drugs, i.e. phenobarbitone or valproate, to prevent seizure recurrences.[1,70] Continuous antiepileptic treatment of children with febrile seizures is generally considered obsolete nowadays, because of the severity of negative side effects (phenobarbitone and valproate) and the questionable efficacy (phenobarbitone).[71-77]

In one large clinical trial intermittent treatment with diazepam in a dose of 1 mg per kg bodyweight per 24 hours administered in 3 eight-hourly doses during fever has been proved efficacious in children with an increased seizure recurrence risk.[78] Accordingly, a smaller trial showed the preventive effectiveness of a lower dose, although one might comment on the possibility of bias due to the random allocation procedure using even and odd days.[79] Other

treatment options were studied because of the side effects of diazepam and because of the less positive results in two smaller studies using a lower dose. We note here that any eventual efficacy of intermittent treatment of recurrent seizures is at least partly reduced due to the inherent problem of the recurrent seizure being the presenting symptom of fever.[78,80-82]

Several clinical studies support the assumption that there is a temperature level above which seizures will develop.[9,64,68,69] From this we may expect that reduction of the body temperature is effective in the prevention of recurrences. Thus a rational alternative option to prevent febrile seizure recurrences is intermittent treatment of the child with antipyretic drugs during fever. Until now no proper evaluation of the efficacy of antipyretic treatment in comparison with placebo to prevent febrile seizure recurrences has been carried out. Three studies investigated the preventive efficacy of antipyretics. None were antipyretic-placebo controlled trials with a standardised antipyretic treatment schedule.[80,83,84] In one study only seizure recurrence within the same fever episode was studied.[84] Despite their methodological flaws all three studies drew the conclusion that antipyretics were not effective in preventing recurrent febrile seizures.

Ibuprofen and acetaminophen are generally used in febrile children. In several studies their antipyretic efficacy and the low risk of side effects have been proved.[85-92] Some of the studies assessing the antipyretic efficacy and the risk of side effects of ibuprofen and acetaminophen in children have excluded children with febrile seizures.[85,86,88,89] In four studies only in-hospital patients were studied.[86,87,90,91] Thus, before investigating the efficacy of antipyretics in the prevention of febrile seizure recurrence, it is necessary to assess the fever-reducing effect in children with febrile seizures. If antipyretics fail to reduce fever in children with febrile seizures it is unlikely that prevention of febrile seizure recurrences can be reached. Therefore, the antipyretic efficacy of ibuprofen 5 mg per kg bodyweight per dose versus acetaminophen 10 mg per kg per dose both to be administered six-hourly during fever was studied in a randomised clinical trial in outpatient children, who visited the Sophia Children's Hospital with febrile seizures in 1991 until 1993.[93] Ibuprofen appeared to be a stronger antipyretic drug especially in the first hours after starting the treatment. In the ibuprofen group 0.5 °C more reduction of the temperature at 4 hours after fever onset was shown. These results are consonant with those of four other studies.[85,87,88,90] The other studies showed no difference in antipyretic efficacy between ibuprofen and acetaminophen.[86,91,92] These results, together with the inconclusive results and methodological flaws of earlier trials assessing the preventive efficacy of intermittent antipyretic treatment, are the rationale to perform a randomised placebo controlled trial of ibuprofen syrup during fever to prevent febrile seizure recurrence: study aim 4, chapter 1.2.

Genetics

The precise eliciting mechanism of febrile seizures is still unknown. We still do not know, why one child develops a febrile seizure during fever, while another seemingly similar child, does not. In general; it is assumed that in young children the vulnerability to develop a seizure is related to the maturation phase of the child's nervous system and the severity of any acute cerebral dysfunction. Furthermore, children may have an inherited (genetically determined) susceptibility to convulsions. Environmental factors may contribute to susceptibility. It is

unclear how these factors interact.[94] Genetic studies of febrile seizures may result in the discovery of predisposing genes. This may lead to an improved understanding of the pathophysiologic mechanisms in febrile seizures and eventually in other seizure disorders.

Febrile seizures are known to aggregate in families. Of all children with febrile seizures, 18 to 40% have affected relatives.[11,60,64,65,69] Twin studies of febrile seizures further supported a genetic contribution, although not all studies confirmed that the concordance rates of monozygotic twins were significantly higher compared to those in dizygotic twins.[95-97] A polygenic aetiology in some families is suggested, an autosomal dominant inheritance pattern has been observed in others.[97,98] One study found different inheritance patterns, depending upon whether or not the patients had suffered recurrent febrile seizures or only one.[99]

Several clinical studies support the role of genetic factors in febrile seizures. It is known that an affected first degree relative (parents/siblings) increases the risk of febrile seizure recurrence.[8,10,11,64] A strong association was defined between the proportion of first degree relatives affected by febrile seizures and the two-years recurrence risk of febrile seizures.[11] The proportion was defined as the number of first degree relatives affected divided by the total number of first degree relatives. If there were no affected first degree relatives, the two-years recurrence risk was 27%; if one or more were affected, up to a proportion of 0.5, this risk was increased to 40%; if the affected proportion was higher than 0.5, e.g. the father and two siblings were affected while the mother was not, the risk to suffer a recurrent seizure within two years was 83%. In addition, this study showed that second and third degree relatives were uninformative. Other investigators have demonstrated that in children with febrile seizures either a first degree family history of febrile seizures or epilepsy or both were predictors of febrile seizure recurrence.[6,12,64]

Two studies have investigated the risk of seizure disorders among relatives of probands with febrile seizures.[60,100] Both studies have assessed the risk of siblings to develop febrile seizures. Further, they have investigated whether characteristics of the probands' febrile seizures and whether a history of febrile seizures in the parents are associated with the risk of the probands' siblings to develop febrile seizures. Both studies defined that this risk increases to 7-10% compared to the risk of 4% in the general population. Sibling risk increases further if the proband has recurrent febrile seizures, if the proband has febrile seizures with complex characteristics and if one or both parents has had febrile seizures.[60,100] Instead of addressing complex seizure characteristics one of these two studies defined young age at onset in the proband associated with increased sibling risk.[100]

These studies support the existence of a genetic predisposition in familial febrile seizures. Based on the results of the clinical studies, there is no doubt that frequent febrile seizure recurrences are genetically determined in familial febrile seizures. Further, complex febrile seizures may also include a familial predisposition.[101] The dissection of the heterogeneous group of children with febrile seizures into subgroups of patients with more homogeneous phenotypes is important. The definition of specific subgroups that are likely to be genetically determined may contribute to the localisation of genes involved in febrile seizures: study aim 7, chapter 1.2.

Studies investigating a specific type of generalised childhood epilepsy called Benign Familial Neonatal Convulsions (BFNC) described that febrile seizures aggregate in BFNC families, which is considered suggestive for a hereditary common origin of both diseases.[102,103] In 1989 BFNC has been linked to genetic markers on chromosome 20q, later in 1993 also on chromosome 8q.[102-106] More recent linkage studies of febrile seizures, however, were unable to verify that BFNC-genes predispose for febrile seizures.[103,107] Another linkage study, however, provided suggestions of a gene on chromosome 8q13-21 involved in febrile seizures.[108] A breakthrough in the research concerning the genetic basis of epilepsy has been the identification of mutations in two novel potassium channel genes (KCNQ2 on chromosome 20q and KCNQ3 on chromosome 8q), which co-segregate with the BFNC-phenotype in a large BFNC family.[109,110] The pathophysiologic basis of the idiopathic generalised epilepsy's may include disturbances in the electrolyte balance between the intra- and extracellular space. These disturbances may be caused by a reduction in function of potassium channels, which may influence the excitability of the nervous system.[111,112]

The chance to find genes predisposing for febrile seizures is increased by searching gene localisations that have been demonstrated to be involved in clinically associated diseases or syndromes: the 'candidate regions'. Candidate regions for febrile seizures are localised genes predisposing for epileptic disorders. Because of the previously reported association between febrile seizures and BFNC and in view of the recent findings, candidate regions of major importance for febrile seizures comprise genes on chromosome 20q and 8q. Therefore, we focused on these chromosomes to study gene localisations involved in febrile seizures: study aim 8, chapter 1.2.[102-106]

Aspects of informed consent

The informed consent procedure plays a central role in clinical studies. Without consent of the patient or his parents no participation of the patient and thus no study results will come about. The role of informed consent, however, has been explored only on a limited scale in pediatric studies.[113-115] Pediatric studies assessing socio-economic status of the parents who permitted their child to participate in clinical research showed conflicting results: they found a similar, higher and lower education and occupation level.[89,113,114] Further, the informed consent information provided is often too difficult and the participants are in a varying degree aware of the details of the study. These results have been shown by questioning adult participants and their families only; comparable data of pediatric studies are lacking. The main motivation to participate in clinical research is to contribute to clinical science.[116-119] In pediatric studies it has been shown that a substantial number of parents is willing to participate, even without being adequately informed about the benefits and risks, and despite the fact that it will cost parents' time and effort.[113,114] With respect to this specific group of parents the role of informed consent is rather limited; they will participate anyway. One study questioned parents about whether or not they would participate with their (new-born) child in the hypothetical situation that such was asked.[114] The results described that 21% of the parents was prepared to participate for the benefit of other children, contribution to clinical science and confidence in physicians. Of the parents questioned, however, 74% would refuse because of the risk of negative side effects and because of the fact that the study medication had not been proved efficacious. It is necessary that more of these data about pediatric studies become available.

We may then be able to improve the quality of the procedures, which will be beneficiary to the participating patients, their parents and the study itself: study aim 9, chapter 1.2.

1.2 Aims of the study

The overall aim of this thesis is to contribute to our knowledge of febrile seizures and thus to the improvement of the quality of health care involving children with febrile seizures. The specific aims of this thesis are to define the diagnostic work-up at presentation of children with seizures associated with fever, to get insight in the impact of febrile seizures on daily life, to improve the prediction of febrile seizure recurrences, to assess the efficacy of intermittent treatment of antipyretics to prevent febrile seizure recurrences, to study the genetic basis of febrile seizures and to evaluate the informed consent procedure in a randomised clinical trial. In this paragraph these aims are further specified.

1. The evaluation of combinations of specific history and physical examination characteristics of children with febrile seizures, that might identify individual children for whom laboratory tests at presentation are unnecessary, has not been performed in previous studies. Such a prediction model for the exclusion of biochemical underlying causes of the seizures may help in the decision whether or not metabolic blood tests are indicated in the individual patient. We compiled prediction models for normal blood levels of calcium, sodium and glucose in individual children with seizures associated with fever, based on the specific combination of their clinical characteristics. The results are given in **chapter 2.1.**

2. The diagnostic value of peripheral leukocyte count in children presenting with febrile seizures is not clear, because in clinical pediatric practice it is often suggested that increased leukocyte counts might be explained by the seizure duration itself. Therefore, the association between peripheral leukocytosis and febrile seizure duration was assessed (**chapter 2.2**).

3. Earlier studies have shown the extent of parental fear as a result of febrile seizures affecting their child. It is not known, however, whether the current provision of information to parents regarding fever and febrile seizure positively changes the parents' attitude. **Chapter 3** gives an current overview of parents' perceptions and beliefs about fever and febrile seizures.

4. Neither continuous treatment with anti-epileptic drugs nor intermittent treatment with diazepam during fever has been proved to be useful for the patient with respect to prevention of febrile seizure recurrences. Intermittent antipyretic treatment is a rational treatment option, but it has never been evaluated properly in a randomised placebo controlled trial. Therefore, we measured the efficacy of ibuprofen to prevent febrile seizure recurrence in a randomised double blind placebo controlled trial, as reported in **chapter 4.**

5. Previous studies assessing the association between the frequency of fever episodes and febrile seizure recurrence contain methodological flaws. We assessed the risk of febrile

seizure recurrence as a function of the number of fever episodes in the first six months after a febrile seizure (**chapter 5.1**).

6. It is of etiologic and practical value to predict a recurrent febrile seizure specifically at the time when children, who have suffered a previous febrile seizure, have got a febrile illness again. Prediction models using actual body temperature and actual age of the child have not been constructed before. We constructed a model using age and temperature at fever onset as predictors of febrile seizure recurrence in the corresponding fever episode. The results are presented in **chapter 5.2.**

7. Genetic studies of febrile seizures aim to increase etiologic knowledge. An important step in localising genes involved in febrile seizures may be the dissection of the heterogeneous group of children with febrile seizures into subgroups of more homogeneous patients with specific phenotypes. We studied whether children with familial febrile seizures have more complex seizure characteristics than children without familial febrile seizures (**chapter 6.1**).

8. Identification of genetic localisation(s) of febrile seizures gains efficiency if 'candidate regions' are studied first, before a complete genomic search is carried out. Because of the suggested relations between febrile seizures and BFNC, major candidates to be studied are chromosome 8q and 20q, which have been associated with BFNC. There are suggestions of a major gene for familial febrile seizures mapping to chromosome 8q. We studied chromosome 8q and 20q to localise genes involved in febrile seizures, using the affected sib pair method. The study results are reported in **chapter 6.2.**

9. Details of informed consent procedures in pediatric studies have been studied only on a limited scale. We do not know why parents permit or refuse participation of their child in clinical research and how well they evaluate specific study details, such as random allocation, negative side effects of the treatment, the burden to their child, and practical issues as investigating time and effort. These data are necessary to improve the quality of the informed consent procedure in pediatric studies in general. We investigated parents' awareness of the study details, their evaluation of the informed consent procedure and their reasons for consenting to their child's participation in a randomised double blind placebo controlled trial of ibuprofen to prevent febrile seizure recurrence (**chapter 7**).

1.3 Study populations

Context of the febrile seizures study

Febrile seizures have been registered prospectively in the Pediatric Department of the Sophia Children's Hospital Rotterdam since 1988.[120,121] In 1994 collaboration started with the Pediatric Department of the Juliana Children's Hospital Den Haag and since then registration has taken place in both hospitals. In the Sophia Children's Hospital, a secondary and tertiary referral hospital, the outpatient clinic department includes mainly (93%) basic specialist

care.[122] The Juliana Children's Hospital is a secondary referral hospital. To both hospitals patients with febrile seizures are referred either by a general practitioner or they come in by themselves. The follow-up of children with febrile seizures has been centred around an outpatients' clinic set up for children with febrile seizures and their parents. Since the start of the registration three physician-investigators (MD) involved in the febrile seizures research project have consecutively run the outpatient clinic hours supervised by two pediatricians (MD, PhD). All patients in the prospective follow up registration visited this outpatient clinic at least once, usually two to four weeks after the febrile seizure had occurred. In the follow-up the child was examined and oral and written information about fever and febrile seizures were provided. Furthermore, baseline characteristics with respect to the febrile seizures of the child, including the family history of febrile seizures and epilepsy were collected. Extra time was available to discuss participation in the running studies and to ask informed consent, if the child met the study requirements.

Study populations of the present studies

The two diagnostic studies described in **chapter 2** comprised children with a seizure associated with fever who were seen at the emergency ward of the Sophia Children's Hospital between 1990 and 1992. All children were prospectively encoded according to the Problem Oriented Patient Classification System that was introduced in the Sophia Children's Hospital in 1988. [122]

Children who visited the Sophia Children's Hospital Rotterdam and the Juliana Children's Hospital Den Haag between 1994 and 1996 were the source population of the randomised double blind placebo controlled trial of ibuprofen syrup to prevent febrile seizure recurrences. All children had visited the febrile seizure outpatient clinic hours (**chapter 4**).

The children who had participated in the randomised controlled trial and had been allocated to the placebo group were included in a febrile seizure recurrence prediction study. To the study assessing the frequency of fever episodes as a risk factor for febrile seizure recurrence in the first six months after a febrile seizure, we added the 'cohort study' population. This population was recruited from all children with a febrile seizure who visited the Sophia Children's Hospital Rotterdam and the Juliana Children's Hospital Den Haag in 1996 and 1997. All children had visited the febrile seizure outpatient clinic hours. Participating children were prospectively followed during six months after the last previous seizure (**chapter 5.1**).

The data of all children who had participated in the randomised controlled trial were also used for a study of the prediction of febrile seizure recurrence in subsequent fever episodes after the last febrile seizure, using temperature and age as predictors. For this study we included both the children who had been allocated to placebo and those who had been allocated to ibuprofen (**chapter 5.2**).

All parents of the children who had participated in the randomised controlled trial of ibuprofen to prevent febrile seizure recurrence were included in a questionnaire study after the trial had been finished. These parents formed the population of the study of parental fear

regarding fever and febrile seizures (**chapter 3**) and aspects of informed consent in pediatric randomised controlled trials (**chapter 7**).

Children were selected from the febrile seizure registration in the two participating hospitals between 1994 and 1996 for the study of the characteristics of familial febrile seizures. The case group consisted of children with a first degree family history of febrile seizures (an affected sibling or parent); the control group included the remaining children who had no first degree relatives affected by febrile seizures (**chapter 6.1**).

For the affected sib-pair analysis of febrile seizures children were selected from the febrile seizure registration since the start in the Sophia Children's Hospital Rotterdam in 1988 until December 1997.[10,11,93] In 1994 the registration started in the Juliana Children's Hospital Den Haag, where eligible patients were recruited until December 1997. Additionally, we selected children with a febrile seizure who visited the Juliana Children's Hospital Den Haag between 1992 and 1994, which was two years before the registration was started there. Children with febrile seizures were only included, if they had one or more brothers or sisters who were also affected by febrile seizures. Because more participating families were required we started collaboration with pediatric departments of regional hospitals and regional general practitioners in January 1997. The pediatricians and general practitioners involved were asked to discuss the study with those parents who had two (or more) children with febrile seizures. In June 1997 we introduced the study in the monthly popular family magazine 'Ouders van Nu'. The responding families which fulfilled the criteria were included. All children whose the parents had given informed consent to study participation, before November 1997, were included in this study (**chapter 6.2**).

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2

Diagnostic aspects

2.1 Seizures associated with fever: clinical data as predictors for normal biochemical blood levels

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Summary

We developed a predictive model to assess the probability of normal biochemical blood test results in children presenting with a seizure associated with fever. The models were based on various combinations of patient characteristics of the history and physical examination of 203 children. The characteristics included gender, age in years, previous history of febrile seizures, family history of febrile seizures, fever previous to the seizure, vomiting and diarrhoea previous to the seizure. Further, clinical characteristics of the seizure were considered: focal seizure signs, multiple seizure, seizure duration and rectal temperature at seizure. The outcome was defined as normal test results of serum levels of sodium (n=115, 68%), calcium (n=149, 89%) and glucose (n=173, 100%), according to the hospital reference values. The prevalence of abnormal test results was rather low and the abnormalities were outside the morbidity range. We used logistic regression to relate the outcome to the several clinical characteristics. The discriminative ability of the models was 0.63 (area under the receiver operating characteristic curve of the model predicting normal sodium), 0.66 (normal calcium) and 0.66 (both normal) The score chart we constructed is an additional tool to a carefully performed patient history and physical examination and it may help to decide if a biochemical test is indicated for the individual patient.

In children with seizures associated with fever, abnormal biochemical blood test results are rare and outside the morbidity range. The biochemical tests are generally not required. In children with a low probability of a normal result as calculated by the score chart, the test may be indicated.

Introduction

In children presenting with a seizure associated with fever biochemical blood tests aim to exclude an underlying disorder which may have contributed to the seizure but is not apparent on taking a patient history and physical examination.[17] If prediction of normal test results would be possible, the number of unnecessary tests may be reduced; only patients with a low probability of normal test results will need to be tested. Previous studies have shown that performing all standard biochemical tests as a routine is useless.[6,7,11,12,16,17,20]

An association between biochemical abnormalities and complex seizure characteristics has been found [10-12,15], implying that children with complex seizure characteristics should be tested.[7] Other patient characteristics studied include age and history of metabolic or gastrointestinal disease.[3,11,12] Recently, recommendations for the diagnostic evaluation of

children with simple febrile seizures have been published.[1] These guidelines are based on the available evidence and conclude that blood laboratory evaluation of the seizure is usually not required.

In accordance with these guidelines, we aimed to study various combinations of patient characteristics to identify children with a low or high risk of normal test results. We used multivariable statistical techniques.[8] The aim of this study was to develop a predictive model to assess the probability of normal blood levels of calcium, sodium and glucose in children with simple and complex seizures associated with fever, based on clinical data available from the history and physical examination of the patient.

Patients and Methods

Patients

Between January 1, 1990 and December 31, 1992, 249 children with a seizure associated with fever were seen at the emergency ward of the Sophia Children's Hospital in Rotterdam. In this hospital a Problem Orientated Patient Classification System has been introduced since 1988, in which prospective encoded registration of reason of referral is carried out routinely.[5] Children between 3 months and 6 years of age were eligible. If the seizure was accompanied by major signs of meningitis such as petechiae, nuchal rigidity or coma, they were encoded as such and therefore did not enter this study. We excluded 46 children because of presentation > 24 hours after the seizure, a history of epilepsy or transfer from another hospital. The study population consisted of 203 children.

Definitions

A febrile seizure was defined in accordance with the National Institutes of Health of 1980.[13] Focal seizures were defined as partial seizures, seizures starting in one limb before secondary generalisation, seizures accompanied by an asymmetrical position of the head or the eyes, seizures accompanied by a Todd paralysis, or a combination of these. Multiple seizures were defined as seizures recurring within 24 hours. Complex seizures were defined as either focal or multiple seizures or seizures with a duration >15 minutes, or a combination of these.

Methods

Individual clinical data were assessed by review of the patient charts: gender, age (in years), previous history of febrile seizures, family history of febrile seizures, fever previous to the seizure, vomiting and diarrhoea previous to the seizure and the clinical characteristics of the seizure: generalised or focal seizures, single or multiple seizures, seizure duration (in minutes) and rectal temperature at seizure (in °C). The obtained clinical data were linked to the computer-documented biochemical blood test results in the hospital information system by the patient identification code.

The outcome parameters of the blood test results were defined as follows. Normal sodium level was defined as ≥ 135 mmol/l, normal calcium level was defined as ≥ 2.20 mmol/l and normal glucose level was defined as ≥ 2.5 mmol/l, according to the hospital reference values.[4]

Results of lumbar punctures, which were performed in 69 (34%) cases, were not analysed. However, there were no positive viral or bacterial cerebrospinal fluid cultures.

Statistical analysis

The associations between each clinical characteristic and each outcome were quantified using univariable logistic regression analysis. In a multivariable model the outcome was predicted by several clinical characteristics. The probability of normal test results was modelled to the clinical characteristics by comparing patients with normal test results to patients with abnormal test results. As the aim of this analysis is prediction, in principle all clinical characteristics were candidates for inclusion in the multivariable analysis.[18] Model reduction was achieved by considering the plausibility of the predictors, the plausibility of the direction of the association and by considering the p-value (<0.50).[8] Odds Ratios (OR) and their 95% confidence intervals were calculated as the association measures. SPSS for Windows (version 6.0, Chicago, Illinois, USA, 1993) and EGRET (statistical package, SERC, Seattle, Washington, USA, 1990) were used for the analysis. The cases with non-performed tests were initially excluded from the analysis. In a secondary analysis, non-performed tests were coded as normal.

Evaluation of model performance

Discriminative ability was assessed using receiver operating characteristic (ROC) analysis. The area under the ROC curve can be interpreted as the probability that the prediction model will assign a higher probability of normal test results to a randomly chosen patient with normal test results than to a randomly chosen patient with abnormal test results. The area ranges theoretically from 0.5 (no discrimination) to 1.0 (perfect discrimination); the higher, the better.

The internal validity of model performance was assessed with bootstrapping techniques. Random bootstrap samples were drawn with replacement from the full sample consisting of all patients (100 replications). The model was estimated on these bootstrap samples and evaluated on the full sample. Moreover, bootstrap estimates were used to derive a shrinkage factor for the final predictive model. This factor corrects the logistic regression model for overoptimism.[8,9]

Results

Study population

Table 2.1.1 shows the distribution of the patient characteristics across the study population. The median age at presentation was 1.5 years and 62% were boys. A positive previous history of a febrile seizure was present in 17% and 11% had a positive first-degree family history of febrile seizures. Fever previous to the seizure was present in 78% and 33% had vomiting and diarrhoea previous to the seizure. Of the children 58% had one or more complex seizure characteristics; focal signs (15%), multiple seizures (32%) and seizure duration >15 minutes (28%). The median rectal temperature at seizure was 40.0 °C.

Table 2.1.1 Distribution of patient characteristics

(n=203)	n (%)
General characteristics	
Male	125 (62%)
Female	78 (38%)
Age in years[a]	1.5 (1.2-2.2)
Febrile seizures	
In patient history	
present	34 (17%)
absent	169 (83%)
In family history[b]	
present	22 (11%)
absent	181 (89%)
Previous symptoms	
Fever	
present	159 (78%)
absent	44 (22%)
Vomiting/diarrhoea	
present	67 (33%)
absent	136 (67%)
Seizure characteristics	
Focal	31 (15%)
Generalised	172 (85%)
Multiple	64 (32%)
Single	139 (68%)
Duration in minutes[c]	
≤ 15	147 (72%)
15-30	26 (13%)
≥ 30	30 (15%)
Temperature in °C[a]	40.0 (39.4-40.4)

[a] Median (25-75 percentiles)
[b] First degree
[c] Used as continuous variable in the model

Laboratory test results

Of all 203 children, 169 underwent a sodium test, resulting in 115 (68%) normal sodium levels and 54 (32%) cases of hyponatriaemia (range: 126-134 mmol/l) (Table 2.1.2). Three of them had a sodium level between 126 and 129 mmol/l. Of the 167 children who underwent a calcium test,

149 (89%) had a normal calcium level and 18 (11%) children had hypocalcaemia (range: 1.90-2.18 mmol/l) (Table 2.1.3). Of 173 who underwent a glucose test, all levels were in the normal range.

Univariable and multivariable analysis
In the univariable analysis, single seizures was the only significant predictor (OR>1) of a normal sodium level at p<0.05 (Table 2.1.2). The other six characteristics indicated a normal sodium level (OR>1), but the association was weak: female gender, older age, previous history of febrile seizures, absence of vomiting or diarrhoea previous to the seizure, generalised seizures and longer seizure duration. The reduced multivariable model included four characteristics as predictors: female gender, previous history of febrile seizures, generalised and single seizures. This multivariable combination constituted a statistically significant model (p=0.004).

In the univariable analysis, absence of vomiting or diarrhoea previous to the seizure and shorter seizure duration were the significant predictors (OR>1) of a normal calcium level at p<0.05 (Table 2.1.3).The other three characteristics indicated a normal calcium level (OR>1), but the association was weak: female gender, younger age and first degree family history of febrile seizures. These five characteristics were retained in the multivariable model (p=0.01).

Because all glucose test results were in the normal range, only the combination of both normal sodium and calcium levels was analysed. Both a sodium and a calcium test was done in 163 children, 98 (60%) cases were in the normal range and 65 (40%) had hyponatriaemia or hypocalciaemia (Table 2.1.4). Two characteristics were univariably significantly associated with the outcome (p<0.05): absence of vomiting or diarrhoea previous to the seizure and single seizures. The other five characteristics were associated with both normal sodium and calcium levels (OR>1), but the association was weak: female gender, previous history of febrile seizures, absence of fever previous to the seizure, generalised seizures and shorter seizure duration. In the multivariable analysis, absence of fever prior to the seizure was excluded and six predictors were included in the model (Table 2.1.4). The multivariable combination was statistically significant (p=0.01).

In an additional analysis, in which the non-performed tests were counted as normal test results, two predictors, which initially were included in the multivariable models, were excluded: female gender in the model predicting normal calcium levels and previous history of febrile seizures in the model predicting both normal sodium and calcium levels. All other predictors were retained in the models, with a similar OR and confidence interval as described previously.

The area under the ROC curve of the model to predict normal sodium levels, normal calcium levels and both normal sodium and calcium levels was 0.66, 0.73 and 0.70, respectively, when evaluated on the same data set used to derive the model. These estimates are generally overoptimistic. Using bootstrapping for internal validation of the models, the areas were reduced to 0.63, 0.66 and 0.66, respectively.

Table 2.1.2 Patient characteristics and normal sodium levels

	sodium levels			
	normal n=115 (68%)	abnormal n=54 (32%)	OR (CI95%) univariable	OR (CI95%) multivariable
General characteristics				
Male	66	37	0.62(0.31-1.23)	0.58(0.28-1.20)
Age in years	1.7(1.2-2.3)[a]	1.4(1.1-2.0)[a]	1.28(0.85-1.93)	-
Febrile seizures				
in patient history	23	6	2.00(0.77-5.23)	1.99(0.72-5.51)
in family history[b]	11	5	1.04(0.34-3.18)	-
Previous symptoms				
Fever	89	44	0.78(0.34-1.78)	-
Vomiting/diarrhoea	36	22	0.66(0.34-1.29)	-
Seizure characteristics				
Focal	16	11	0.63(0.27-1.46)	0.54(0.22-1.30)
Multiple	29	27	0.34(0.17-0.68)[d]	0.33(0.17-0.66)[d]
Duration in minutes[c]			1.23(0.78-1.93)	-
≤ 15	80	41		
15-30	14	6		
≥ 30	21	7		
Temperature in °C	40.0(39.4-40.5)[a]	40.0(39.7-40.4)[a]	0.90(0.62-1.31)	-

[a,b,c,d] See Table 2.1.4

Table 2.1.3 Patient characteristics and normal calcium levels

	calcium levels			
	normal n=149 (89%)	abnormal n=18 (11%)	OR (CI95%) univariable	OR (CI95%) multivariable
General characteristics				
Male	90	12	0.76(0.75-2.15)	0.63(0.21-1.93)
Age in years	1.5(1.2-2.2)[a]	1.7(1.2-2.6)[a]	0.78(0.47-1.30)	0.75(0.44-1.27)
Febrile seizures				
in patient history	26	3	1.06(0.29-3.94)	-
in family history[b]	12	4	0.31(0.09-1.09)	0.30(0.07-1.28)
Previous symptoms				
Fever	116	14	1.00(0.31-3.24)	-
Vomiting/diarrhoea	46	10	0.36(0.13-0.98)[d]	0.38(0.13-1.10)
Seizure characteristics				
Focal	22	3	0.87(0.23-3.23)	-
Multiple	49	7	0.77(0.28-2.09)	-
Duration in minutes[c]			0.43(0.25-0.74)[d]	0.43(0.24-0.76)[d]
≤ 15	112	8		
15-30	17	2		
≥ 30	20	8		
Temperature in °C	40.0(39.4-40.4)[a]	39.9(39.3-40.3)[a]	1.09(0.63-1.89)	-

[a,b,c,d] See Table 2.1.4

Table 2.1.4 Patient characteristics and both normal sodium and calcium levels

	sodium and calcium levels			
	normal n=98 (60%)	abnormal n=65 (40%)	OR (CI95%) univariable	OR (CI95%) multivariable
General characteristics				
Male	54	45	0.55(0.28-1.07)	0.47(0.23-0.95)[d]
Age in years	1.6(1.2-2.2)[a]	1.5(1.1-2.1)[a]	1.08(0.74-1.57)	-
Febrile seizures				
in patient history	20	9	1.60(0.68-3.79)	1.59(0.63-3.99)
in family history[b]	9	7	0.84(0.30-2.37)	-
Previous symptoms				
Fever	74	54	0.63(0.28-1.41)	-
Vomiting/diarrhoea	27	29	0.47(0.24-0.92)[d]	0.54(0.27-1.09)
Seizure characteristics				
Focal	13	13	0.61(0.26-1.42)	0.68(0.27-1.71)
Multiple	25	31	0.38(0.20-0.74)[d]	0.42(0.21-0.85)[d]
Duration in minutes[c]			0.83(0.55-1.25)	0.81(0.53-1.25)
≤ 15	72	45		
15-30	12	6		
≥ 30	14	14		
Temperature in °C	40.0(39.4-40.6)[a]	39.9(39.4-40.4)[a]	0.98(0.69-1.39)	-

[a] Median (25-75 percentiles)
[b] First degree
[c] Used as continuous variable in the model
[d] Significant at $p<0.05$

Score chart

We presented the multivariable models in a score chart (Table 2.1.5). This chart is intended to facilitate the estimation of the probabilities of normal sodium and calcium levels in clinical practice. Scores for each predictor were derived from the logistic regression coefficients, which were reduced by a correction for overoptimism. This correction was assessed by bootstrapping, which resulted in a shrinkage factor of 0.81 in the model predicting normal sodium levels, 0.79 in the model predicting normal calcium levels and 0.80 in the model predicting both normal sodium and calcium levels. The scores were subsequently multiplied by 10 and rounded to whole numbers. The scores corresponding to the values of the predictors for the individual patient can be filled in on the score chart. The corresponding probabilities can be read from Figure 2.1.1. Alternatively, the exact probabilities can be calculated using formulas (see Appendix).

Table 2.1.5 Score chart to estimate the probability of normal biochemical blood test results[a]

	value		
	normal sodium	normal calcium	normal sodium and calcium
General characteristics			
Female gender	5	4	6
Age in years			
≤1.5	-	5	-
1.5-2.5	-	3	-
≥2.5	-	0	-
Febrile seizures			
Present in patient history	6	-	4
Absent in family history	-	9	-
Previous symptoms			
Absent vomiting/diarrhoea	-	8	5
Seizure characteristics			
Generalised	4	-	3
Single	9	-	7
Duration in minutes			
≤ 15	-	13	4
15-30	-	7	2
≥ 30	-	0	0
Sumscore: (add variables that apply)			

[a] We illustrate the use of the score chart with a hypothetical patient, a boy aged 2 years, presenting with a multiple seizure associated with fever, without focal signs, duration 5 minutes, without vomiting or diarrhoea previous to the seizure. The patient's history includes one febrile seizure. The family history is negative for febrile seizures. The sumscores are 10 (6+4) for normal sodium, 33 (3+9+8+13) for normal calcium and 16 (4+5+3+4) for both normal sodium and calcium. From Figure 1 it can be approximately seen that our patient has a probability of around 65% of a normal sodium level, 95% of a normal calcium level and 60% of both a normal sodium and calcium level. The exact probabilities (using the formulas) are 62%, 95% and 59%, respectively. One might suggest that no laboratory tests are indicated in this patient, since abnormal test results are unlikely.

Discussion

We confirmed earlier findings that severe hyponatriaemia, hypocalciaemia and hypoglycaemia, severe enough as to be considered the cause of seizures is rare. We have found only three cases of severe hyponatriaemia. All other abnormalities of sodium and calcium levels were mild and all glucose levels were within the normal range. Earlier studies showed that sodium, calcium and glucose blood tests in children with seizures associated with fever resulted in a very low number of abnormal results, in particular in children with 'simple' (non-complex) seizures.[6,7,11,12,16,17,20] However, some authors state that a glucose and calcium test should be done, because these are treatable conditions and the tests are relatively inexpensive.[21] Based on the results of earlier studies.[6,20] they calculated the risk of abnormal glucose and calcium levels as 3 in 1000 and concluded that sodium tests are indicated only in case of suspicion of

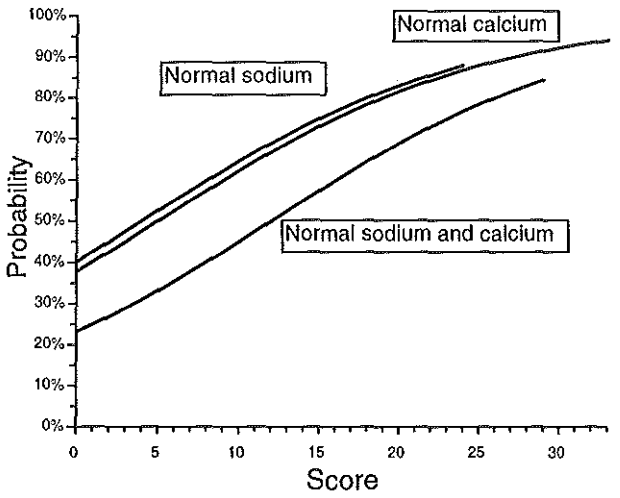

Figure 2.1.1 Predicted probabilities corresponding to the sumscores as calculated with the score chart (see Table 5 and text)

disturbances in the milieu interne.[21] Other authors concluded also that biochemical tests are useful, if they have been performed on indication. The indications they found were multiple-type seizures, status epilepticus, history of metabolic or gastrointestinal disease and young age.[3,7,10,11,12,15,17] These indications, which imply an increased risk of abnormal test results, have been confirmed quantitatively by our analysis.

In agreement with earlier studies, vomiting or diarrhoea previous to the seizure was associated with biochemical abnormalities.[11,12,21] We included this characteristic in the model predicting normal calcium levels and in the model predicting both normal sodium and calcium levels. The presence of vomiting or diarrhoea previous to the seizure was not very important after inclusion of other predictors in the multivariable model predicting normal sodium levels. This means that other predictors were stronger associated with the outcome. In accordance with the results of earlier studies, we have found a rather strong association between complex seizure characteristics and abnormal sodium levels.[10-12,15] The absence of the predictor 'vomiting or diarrhoea' in the multivariable model predicting normal sodium levels may also be partially explained by our relatively mild definition of the predictor: if children had vomited only once before the seizure occurred, it was counted as previous complaints of vomiting or diarrhoea. If we had defined it as a duration of at least two days we might have found the association.

Limitations

A limitation of our study is that not all cases were biochemically tested, which might result in a selection bias. However, compared to the two other studies reporting the number of patients tested, our study included a similar or even larger percentage of children who were tested.[7,17] We have studied the data firstly by leaving the missing data out of the model and secondly, by counting the missing data as normal test results. We found similar results for the prediction

models. We conclude that our results apply to the entire study population. Based on the aim of the study, which is to assess the probability of normal biochemical blood test results in children presenting with a seizure associated with fever, we have lost some information by analysing the laboratory test results as dichotomous variables (abnormal or normal) while the original laboratory test results were continuous. Furthermore, our sample size was limited and the statistical models we have constructed require further validation.

Practical application

The multivariable models were presented in a score chart. For sodium test results, an individual patient can have a score between 0 and 24, corresponding with a probability range between 40% and 88%. For normal calcium levels, the score range is between 0 and 39, corresponding with probabilities between 38% and 95%. For both normal sodium and calcium levels the score range is between 0 and 29, corresponding with probabilities between 23% and 85% (Table 2.1.5, Figure 2.1.1). The smaller range of predicted probabilities corresponds to the lower discriminative ability of the model predicting normal sodium levels (area under the ROC-curve 0.63) compared to the models predicting normal calcium and both normal sodium and calcium. These models have a wider probability range, which corresponds to a *slightly* larger area under the ROC-curve (both 0.66).

The definition of a probability selection threshold in performing electrolyte and glucose tests in children presenting with a seizure associated with fever requires a weighing of the benefits and risks. The risks of a test include a short period of minor pain which will frighten the child, the time-delay before the child can be sent home, the low risk of a bone infection and the financial costs. However, if abnormal levels are present, the child will benefit from testing. The detected abnormalities will indicate start of intervention. In mild cases, intervention will comprise re-testing until the abnormal level has normalised. In the rare severe cases, further diagnostic procedures and treatment will be started. If the tests are not performed, hypocalciaemia, hypoglycaemia and hyponatriaemia may be missed. In most cases the missed abnormalities will be outside the morbidity range. Severe biochemical disturbances may result in a long-lasting status epilepticus and cerebral damage.[2,3] In general, the advantages of performing biochemical blood tests may not balance the disadvantages. Decision analysis may help to find the optimal probability of the outcomes estimated using our prediction models, at which probability level the balance between the costs and benefits is most favourable.[14]

We have included patients with seizures associated with fever without any other serious condition, such as suspicion of meningitis or respiratory insufficiency for which hospital transfer is required. Thus, we had a patient group with a seizure associated with fever but without apparent symptoms or signs of an underlying disorder, which is exactly the patient group that is most difficult for clinicians regarding the decision whether or not to perform biochemical blood tests. Our study complements the recommendations to refrain from routine determinations of serum electrolytes and calcium in children with simple febrile seizures, as stated by the American Association of Pediatrics in 1996.[1] Additionally, we have not only studied children with simple febrile seizures, but also children with complex seizure characteristics. We have confirmed and quantified that complex seizure characteristics include an increased risk of abnormal biochemical blood test results. Although the models are limited regarding their discriminative ability, in daily clinical practice the score charts give a hand, at least to the young and inexperienced physician, to decide whether or not biochemical tests are

indicated. However, it should also be clear that the score chart is only an additional tool to a carefully performed patient history and physical examination.

Appendix

The exact formulas to calculate the sumscores are:
Sumscore (normal sodium level)=
1.5-0.6(male gender)+0.7(febrile seizures present in patient history)-0.5(focal seizure type)-1.1(multiple seizure type)

Sumscore (normal calcium level)=
4.1-0.5(male gender)-0.3(age)-1.2(febrile seizures present in family history)-0.5(previous symptoms of vomiting/diarrhoea)-0.8(seizure duration)

Sumscore (normal sodium and calcium level)=
1.5-0.7(male gender)+0.5(febrile seizures present in patient history)-0.6(previous symptoms of vomiting/diarrhoea)-0.4(focal seizure type)-0.9(multiple seizure type)-0.2(seizure duration)

Probability=$1 / [1 + e^{-(\text{sumscore})}]$

The variable 'gender' is 1 for males and 0 for females, the variables 'febrile seizures present in patient history', 'febrile seizures present in family history', 'previous symptoms of vomiting/diarrhoea', 'focal seizure type', 'multiple seizure type' are 1 if true and 0 if false, the variable 'seizure duration' is 0 if ≤ 15, 1 if 16-29 and 2 if ≥ 30 minutes and for the variable 'age' (in years) the value can directly be filled in the formula.

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2.2 The duration of febrile seizures and peripheral leukocytosis

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Summary

In 203 consecutive children with febrile seizures, no clear association (Odds Ratio 1.0 [95% Confidence Interval 0.9-1.1], p=0.59) was found between seizure duration and blood leukocytosis ($\geq 15.0*10^9$ cells/l). Increased leukocyte counts may be misinterpreted because of seizure duration. In children with febrile seizures, leukocyte counts should be used to evaluate the underlying cause of fever.

Introduction

In children with seizures associated with fever, peripheral leukocyte counts are often determined to evaluate the source of the fever.[1] However, in clinical pediatric practice it is suggested that an increased leukocyte count, without any other obvious clinical signs or symptoms indicating a bacterial infection, might be explained by the seizure duration itself rather than by the nature of the infection.

The concept of seizures changing the peripheral leukocyte count is based on previous findings. Generally, stress mechanisms, which may result from the seizure, may increase the leukocyte count. In animal studies stress induced redistribution of leukocytes, resulting in increased blood leukocyte counts, has been demonstrated.[2] In adult patients, long lasting convulsions without fever are associated with peripheral leukocytosis.[3,4] However, other studies did not show changes in leukocyte counts after prolonged seizures.[5] The diagnostic utility of peripheral leukocytosis in children with long-lasting febrile seizures is unclear.

The aim of this study was to assess the association of the leukocyte count and the seizure characteristics in children with febrile seizures, irrespective of the underlying cause of the fever.

Patients and Methods

Patients

We assessed the data of 203 consecutive patients, aged 3 months to 5 years, who visited the Sophia Children's Hospital Rotterdam between January 1, 1990 and December 31, 1992, with a seizure associated with fever. In a previous study we developed a predictive model for biochemical blood test results in children with seizures associated with fever.[6] Febrile seizures were defined according to the National Institutes of Health Consensus of 1980.[7] Children were

excluded if their seizures were accompanied by major signs of meningitis such as petechiae, nuchal rigidity, or coma.

Methods

The characteristics of the seizure were assessed by review of the patient charts: presence of focal seizure signs, multiple type seizure, seizure duration (in minutes), febrile status epilepticus, and temperature at seizure (in °C). These data were linked to the results of the peripheral blood leukocyte counts. In children with febrile seizures, leukocyte counts were used to be performed routinely to evaluate the fever. According to previous studies in children with febrile seizures, leukocytosis was defined as a leukocyte count of $\geq 15.0*10^9$ cells/l.[8,9] Results of lumbar punctures (n=69) were not analyzed; however, there were no positive cerebrospinal fluid cultures. In this analysis the underlying causes of fever were not addressed.

Statistics

Leukocyte counts are given in median values with the 25th and 75th percentiles between brackets. The relation between the seizure characteristics and leukocytosis was estimated using logistic regression analysis. Odds Ratios were used as the measure of association; associations were statistically significant ($p<0.05$) if the 95% Confidence Interval of the Odds Ratio did not include the value 1. The missing test results were initially excluded from the analysis; in a secondary analysis, they were counted as normal. In cases of febrile status epilepticus, leukocyte counts were analyzed by using a non-parametric test.

Results

The study population comprised 125 (62%) boys and 78 (38%) girls; they were median 1.5 (25th-75th percentiles 1.2-2.2) years of age. The seizure characteristics are shown in Table 2.2.1.

Table 2.2.1 Seizure characteristics versus blood leucocyte count (n=203)

Seizure characteristics	Total	Blood leucocyte count		OR (CI95%) univariable	p-value
		$<15*10^9$ cells/l n=129 (64%)	$\geq 15*10^9$ cells/l n=74 (36%)		
Focal type[a]	31 (15%)	19	12	1.1 (0.5-2.5)	0.78
Multiple type[b]	64 (32%)	40	24	1.1 (0.6-2.0)	0.83
Duration in minutes	9 (4-15)	10 (3-15)	5 (4-15)	1.0 (0.9-1.1)	0.59
FSE[c]	30 (15%)	20	10	0.9 (0.4-1.9)	0.70
Temperature in °C[d]	40.0 (39.4-40.4)	40.0 (39.5-40.3)	40.0 (39.2-40.5)	0.9 (0.7-1.3)	0.68

Durations and temperatures are given in median values with 25th to 75th percentiles.
OR=Odds Ratio; *FSE*=Febrile status epilepticus
[a] Focal onset and/or postictal Todd's paresis of facial muscles or limbs.
[b] Seizure recurrence within 24 hours.
[c] Seizure duration ≥30 minutes.
[d] Temperature measured closest to seizure time as documented in the emergency room or in the patient history.

Of all 203 children, 197 (97%) had a leukocyte count performed; the counts were 12.8 (8.5-18.8)*10^9 cells/l, leaving 6 (3%) missing test results. Leukocytosis was found in 74 (36%) children, with counts of 20.6 (17.8-24.2)*10^9 cells/l. This is similar to rates previously published.[8,9] Normal leukocyte counts were found in 123 (61%) children: 9.1 (7.5-12.2)*10^9 cells/l.

We did not find a significant association of any of the seizure characteristics and leukocytosis. Therefore, a multivariable analysis was not performed. If the 6 missing leukocyte counts were coded as normal, the same results were found (Table 2.2.1).

In patients with febrile status epilepticus, leukocyte counts after seizures of more than 45 minutes (n=14, 8.8 (6.7-20.3)*10^9 cells/l) were not significantly different (p=0.10, Mann-Whitney U test) from those after seizures of 30 to 45 minutes (n=16, 13.9 (11.3-19.5)*10^9 cells/l).

Discussion

The results of this study demonstrated that the leukocyte count in the peripheral blood is not significantly related to the duration of the seizure or any other seizure characteristics. Besides assessing the underlying cause of the fever, leukocyte counts are rarely useful as a diagnostic tool in children with seizures associated with fever.[1,7-9] Furthermore, in children with shigellosis, no relation was shown between an increased leukocyte count and the occurrence of a febrile seizure.[10] The major indication for performing a leukocyte count is the clinical suspicion of a bacterial infection that requires treatment, based on findings of the patient history and physical examination.[1]

We conclude that it is unlikely that there is a clear association between seizure duration and blood leukocyte counts in children with febrile seizures. Leukocytosis should not be misinterpreted as due to a long-lasting febrile seizure. Similar to the diagnostic procedure in other children with fever, leukocyte counts should be used in the assessment of fever in children with a febrile seizure.

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3

Parental perception and experience

3 Parents' fear regarding fever and febrile seizures

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Summary

Objective To improve the effectiveness of information, we aimed to understand parents' perceptions and knowledge about fever and febrile seizures. We determined how parents of children with febrile seizures perceive fever and febrile seizures affecting their child.
Methods We carried out a questionnaire study among the parents whose children (n=230) participated in a randomised controlled trial of ibuprofen to prevent recurrent febrile seizures. Of the 230 parents, 181 (79%) responded to the questionnaire.
Results Of all parents, 45% were afraid or very afraid of fever, which was strongly associated with being afraid of recurrent febrile seizures. Parents of children with a non-West European background were more afraid. The consequences of parental fear included frequent temperature measurements (25% measured five times per day or more), sleeping in the same room (24%) and 13% remained awake at night during fever. Witnessing a febrile seizure is a very frightening experience for parents; a majority thought that febrile seizures are harmful, because they look dangerous and 47% thought their child was dying during the initial febrile seizure. On the other hand, reassuring information may be helpful: 21% mentioned it as their reason to consider febrile seizures not harmful.
Conclusion We conclude that parental fear of fever and febrile seizures is a major problem with several negative consequences for daily family life. Adequate provision of information may reduce parental fear. We suggest that information about fever and febrile seizures should be provided to all parents, preferably during their contact with the preventive health care providers. The parents of children with a non-West European origin need extra attention.

Introduction

Young children are frequently affected by febrile illnesses, mostly due to infections without serious consequences. Fever in a young child is a frequent reason for parents to consult the general practitioner or the hospital emergency room. Many parents of young children are worried about fever; they fear a severe illness, adverse effects of the fever itself or, if they are known with the phenomenon, a febrile seizure.[1,2,3] In general, febrile seizures are harmless to the child[4], but any physician who has been involved, may know that the parents perceive the seizure as a very frightening event.

Better understanding of parents' perceptions and beliefs about fever and febrile seizures may promote satisfactory communication and improve the effectiveness of the information provided.[3] To determine how parents of children with febrile seizures perceive fever and febrile seizures affecting their child, we performed a questionnaire study among the parents

whose children participated in a randomised controlled trial of ibuprofen to prevent recurrent febrile seizures.

Patients and Methods

Patients

The study population consisted of the parents who had volunteered their child (n=230) for a randomised double blind placebo controlled trial of ibuprofen to prevent febrile seizure recurrences, of which the results have been reported elsewhere.[5] The trial protocol was approved by the relevant research ethics committees. The children were aged between one and four years old, they had an increased risk of febrile seizure recurrences and all parents were Dutch or English speaking. Each child had visited the emergency room of the Sophia Children's Hospital in Rotterdam or the Juliana Children's Hospital in The Hague, The Netherlands, because of a febrile seizure.

Methods

Two weeks after their febrile seizure, each child visited the special febrile seizure outpatients' clinic, where the investigator provided oral information about fever and febrile seizures to all parents. Additionally, an information leaflet was provided. The matters covered included the prevalence of febrile seizures, the risk of seizure recurrence, the benign nature of febrile seizures in general and the description of the typical attack. The parents of eligible children were informed about the trial and they were asked to give written informed consent; 230 parents consented to participate in the trial. Median 1.4 (25-75 percentiles 1.1-2.1) years after entering the trial, these parents received a letter to introduce the questionnaire study. At that moment their participation in the trial had stopped. If they were willing to participate, we sent a questionnaire and written instructions. The parents of 15 (7%) children were not contacted because they were lost to follow up (n=13), or they participated in another febrile seizures research project (n=2). Thirty-four (15%) did not respond to our announcement and request, without giving a reason. Two questionnaires were returned incomplete. The study population consisted of the parents of 181 (79%) children.

We compiled a questionnaire consisting of structured and semi-structured questions. The questions involved included the following issues: the parents' current perception of fever, the measures they currently take when their child has a febrile illness, and what they considered as their major source of information regarding fever. Furthermore we asked how they had perceived the initial febrile seizure of their child in the past, and how they currently perceive their child's febrile seizures. The questionnaire comprised also several issues about the informed consent procedure and the parents' sociodemographic baseline characteristics; the results have been reported previously.[6] Also baseline characteristics of the child and clinical characteristics of the initial febrile seizure were collected.

Completed questionnaires were coded and analysed using SPSS version 6.0.[7] The answers were categorised in groups. Sociodemographic characteristics were defined in categories[8,9], the details are described in the previous report.[6] High occupation level included intermediate, higher or scientific profession. Low occupation level included elementary or lower profession and no profession/housewife. High education level was defined as higher general secondary or

pre-university education, intermediate or high level vocational training or university education. Low education comprised elementary school, lower general secondary education or lower level vocational training. Continuous variables (i.e. age and temperature data) were reported in median values with 25 and 75 percentiles.

Associations were studied using logistic regression models. Odds Ratios (OR) were given with their 95% confidence interval (CI95%). Associations were statistically significant, if the 95% confidence interval of the OR did not include the value one. Multivariable analysis was performed using stepwise backward regression ($p<0.10$) to identify the most important characteristics associated with the answers. The univariably significant variables were labelled in the tables, with the multivariable OR's given in the text.

Results

Fever

Of all responding parents, 24 (13%) were not and 76 (42%) were a little afraid of fever, 43 (24%) were afraid and 38 (21%) were very afraid. The answers were categorised in two groups: less afraid (n=100) and more afraid (n=81) of fever (Table 3.1). Table 3.1 also shows the baseline characteristics of the 181 responding parents and their children. To determine important characteristics of parents being more afraid, we analysed all baseline characteristics with respect to association with being more afraid of fever (Table 3.1). In the multivariable model, non-West European origin of the child was the strongest characteristic (OR=4.4 (CI95% 1.4-14.3), p=0.01).

Table 3.2 shows the parents' current perceptions of fever, including their expectations of further consequences of high fever. The temperature they considered to be *high* fever differed significantly: parents who were more afraid of fever considered *high* fever median 0.5 °C lower compared to the parents who were less afraid.

The parents were asked to indicate the frequency of measuring their child's temperature and which other extra measures they usually take when the child suffers fever (Table 3.3). In a multivariable model, we analysed which of all measures described in Table 3.3 were associated with being more afraid of fever. We found four: the frequency of temperature measurements per day during fever (OR=2.2 (CI95% 1.2-3.7), p=0.01), taking extra other measures if the child has fever (OR=9.0 (CI95% 1.1-71.1), p=0.04), sleeping in the same room (OR=2.2 (CI95% 1.0-4.9), p=0.04) and remain awake at night (OR=3.6 (CI95% 1.2-11.0), p=0.03).

We determined the parents' major source of information regarding fever by asking: 'In your view, who provided you the most important information concerning fever?'. Their responses were: the hospital, including the febrile seizure outpatient clinic (64%), the general practitioner (8%), the child health centre (2%) and other (26%). No clear differences were found with respect to West European or non-West European origin.

Table 3.1 Baseline characteristics of the parents and children versus being afraid of fever

	Total	Less afraid	More afraid	OR (CI 95%)
Mothers	**n=181**	**n=100**	**n=81**	**univariable**
Age in years	32.6 (29.0-37.0)	32.9 (30.2-36.8)	32.4 (28.7-37.2)	1.0 (0.9-1.0)
Non-West European origin	46 (25%)	11 (11%)	35 (43%)	5.0 (3.3-10.0)
Low education level	77 (43%)	35 (35%)	42 (52%)	2.0 (1.1-3.3)
Low profession level	99 (55%)	44 (44%)	55 (68%)	2.5 (1.4-5.0)
Fathers	**n=155**	**n=87**	**n=68**	
Age in years	35.6 (31.6-39.5)	35.6 (31.6-38.7)	35.6 (31.2-41.4)	1.0 (1.0-1.1)
Non-West European origin	34 (22%)	6 (7%)	28 (41%)	
Low education level	60 (39%)	29 (33%)	31 (46%)	
Low profession level	39 (25%)	22 (25%)	17 (25%)	
Children	**n=181**	**n=100**	**n=80**	
Single-parent family	26 (14%)	13 (13%)	13 (16%)	1.3 (0.6-2.9)
Age in years	3.4 (2.7-4.3)	3.3 (2.7-4.2)	3.5 (2.7-4.3)	0.9 (0.7-1.3)
Female gender	69 (38%)	38 (38%)	31 (38%)	1.0 (0.6-1.8)
Non-West European origin	55 (30%)	12 (12%)	43 (53%)	10.0 (3.3-10.0)[a]
First degree family history of febrile seizures	36 (20%)	19 (19%)	17 (21%)	1.1 (0.5-2.4)
Initial febrile seizure:				
Multiple type	71 (39%)	36 (36%)	35 (43%)	1.3 (0.7-2.5)
FSE[b]	16 (9%)	10 (10%)	6 (7%)	0.7 (0.3-2.1)

[a] Significant in the multivariable model (see text)
[b] *FSE* Febrile status epilepticus: seizure duration ≥30 minutes
rc reference category

Table 3.2 Parental perceptions of fever

	Total (n=181)	Less afraid (n=100)	More afraid (n=81)	OR (CI95%)
Level of temperature				
Considered *high* fever[a]	39.5 (39.0-40.0)	39.5 (39.0-40.0)	39.0 (38.5-40.0)	0.6 (0.4-1.0)[b]
Maximum if untreated[a]	41.0 (40.5-42.0)	41.0 (40.5-42.0)	41.0 (40.0-42.0)	1.0 (0.7-1.4)
High fever harmful				
No	69 (38%)	43 (43%)	26 (32%)	rc
Yes	68 (38%)	32 (32%)	36 (44%)	1.7 (0.9-3.9)
Do not know	44 (24%)	25 (25%)	19 (23%)	rc
Further consequences of high fever				
Febrile seizures	142 (79%)	74 (74%)	68 (84%)	1.8 (0.9-3.9)
Other[c]	23 (13%)	17 (17%)	5 (6%)	rc
None	7 (4%)	5 (5%)	2 (2%)	rc
Do not know	9 (5%)	4 (4%)	5 (6%)	rc

[a] temperature in °C
[b] significant at $p<0.05$
[c] other consequences mentioned were:
braindamage (n=6), drowsiness (n=6), cardiac surmenage (n=3), dehydration (n=3), consequences depend on the cause of fever (n=3) and fever is useful (n=1)

Table 3.3 Measures during the child's fever

	Total (n=181)	Less afraid (n=100)	More afraid (n=81)	OR (CI95%) univariable
Temperature measurements[a]:				2.4 (1.4-4.0)[b]
not more than once (1)	13 (7%)	8 (8%)	5 (6%)	
two to four times (2)	122 (67%)	77 (77%)	45 (56%)	
five to eight time (3)	38 (21%)	14 (14%)	24 (30%)	
more than eight times (4)	8 (4%)	1 (1%)	7 (9%)	
Other extra measures	163 (90%)	83 (83%)	80 (99%)	16.4 (2.1-125.8)[b]
Extra measures[c]:				
use of the baby intercom	28 (16%)	15 (15%)	13 (16%)	1.1 (0.4-2.4)
leave the door open	41 (23%)	24 (24%)	17 (21%)	0.8 (0.4-1.7)
sleep in the same room	44 (24%)	15 (15%)	29 (36%)	3.2 (1.5-6.4)[b]
sleep in the same bed	61 (34%)	26 (26%)	35 (43%)	2.2 (1.2-4.1)
remain awake at night	23 (13%)	5 (5%)	18 (22%)	5.4 (1.9-15.4)[b]
frequently look to check	80 (44%)	40 (40%)	40 (49%)	1.5 (0.8-2.6)
put diazepam ready for use	10 (6%)	6 (6%)	4 (5%)	0.8 (0.2-3.0)
keep the child cool	14 (8%)	8 (8%)	6 (7%)	0.9 (0.3-2.8)

[a] Frequency of temperature measurements per 24 hours; analysed as a continuous variable; values between brackets; the OR represents the risk of being more afraid increasing 2.4 per temperature measurement category

[b] remained significant in the multivariable analysis (see text)

[c] more than one option possible

Febrile seizures

The parents described in their own words what they had thought at the moment their child had its first febrile seizure (Table 3.4). We determined if there were important characteristics of the parents who thought their child had been dying (n=85), using the characteristics given in Table 3.1. A negative independent association was found with initial febrile status epilepticus (OR=0.2 (CI95% 0.1-0.9), p=0.04), which implies that parents who have a child that suffered from an initial long lasting seizure, less frequently think their child has been dying. The parents who had recognised a febrile seizure (n=23), did not differ with respect to any baseline characteristics mentioned in Table 3.1.

We investigated if parents had sought medical help after their child's initial febrile seizure: 173 (96%) of the parents sought immediately for medical help: 100 (55%) dialled the national emergency alarm number, 44 (24%) parents called or visited a general practitioner and 29 (16%) brought their child directly to the hospital. Eight (4%) parents did not seek medical help; they called their neighbours or bystanders for first aid.

We asked the parents whether or not they currently thought, that febrile seizures were harmful. The results are given in Table 3.5. Seventy-four (41%) parents said febrile seizures were harmful, because their child's seizures had looked very damaging; some parents mentioned the possible lack of oxygen during the seizure as harmful; their child had stopped breathing or got cyanotic and 11 (6%) said that after the seizure their child had looked injured. Among the parents who thought that febrile seizures were not harmful (n=79, 44%), 38 said so because they said to have had received convincingly reassuring information that febrile seizures are not harmful.

Table 3.4 Parental thoughts at the moment of their child's initial febrile seizure

n=181	Number (%)
Child is dying	85 (47%)
Recognition of a febrile seizure	23 (13%)
Something very dangerous	20 (11%)
Epilepsy	15 (8%)
Suffocation	15 (8%)
Child is playing a crazy trick	5 (3%)
Other[a]	4 (4%)
Do not know	7 (4%)

[a] including paralysis (n=1), meningitis (n=1), sunstroke (n=1) and pain (n=1)

All baseline variables mentioned in Table 3.1 were studied: low-level profession of the mother was significantly associated with considering febrile seizures as harmful (OR=2.2 (CI95% 1.1-4.6), p=0.03).

Finally, we asked the parents, whether or not they currently were afraid of recurrent febrile seizures affecting their child again: 102 (56%) parents were not or a little afraid and 79 (44%) were afraid or very afraid. Analysing all baseline characteristics from Table 3.1, being afraid or very afraid of new febrile seizures was associated in the multivariable model with low-level profession of the mother (OR=2.3 (CI95% 1.1-5.1), p=0.03), non-West European background of the child (OR=6.8 (CI95% 2.7-17.4), p<0.001) and multiple type initial febrile seizure (OR=2.6 (CI95% 1.2-5.8), p=0.02). We found a very strong significant association between being afraid or very afraid of new recurrent febrile seizures and being afraid of fever: OR=82 (CI95% 31-218), p<0.001. The number of discordant pairs in the two-by-two table may illustrate this large OR: only 10 parents were more afraid of fever while less afraid of a recurrent seizure; 8 were less afraid of fever while more afraid of a recurrent seizure.

Discussion

Half of the responding parents was afraid or very afraid of fever affecting their child. The parents mentioned in 79% the risk of a seizure recurrence as the major consequence of fever and their fear of high fever was strongly associated with their fear of a febrile seizure recurrence. Being afraid of fever was clearly associated with a non-West European background of the child; being afraid of new recurrent seizures showed to be related to a low-level profession of the mother, a non-West European background of the child and a multiple type initial seizure. The results of two other questionnaire studies about fever in children showed, that the occurrence of febrile seizures during high fever is a major issue for parents.[1,2] One study investigated the fear of parents of children who visited a university-based walk-in clinic for several reasons: 15% mentioned a febrile seizure as the main consequence of high fever.[1] The other study included parents whose child was feverish meanwhile: 48% addressed the possibility of a febrile seizure as the principal danger.[2]

Only parents whose child had an increased risk of febrile seizure recurrence and had participated in a randomised controlled trial to prevent recurrences were included. Of the

Table 3.5 Parental thoughts about harmfulness of febrile seizures

n=181	Number (%)
Seizures are harmful	**97 (54%)**
seizures look damaging	74 (41%)
told so by others	12 (7%)
child looked damaged after a seizure	11 (6%)
Seizures are not harmful	**79 (44%)**
information provided was convincing	38 (21%)
own experience	24 (13%)
benign effect of a febrile seizure	5 (3%)
reassuring electroencephalogram	1 (1%)
certain without further specification	11 (6%)
Do not know	**5 (3%)**

parents of 275 children who initially fulfilled the criteria of the randomised controlled trial, the parents of 181 (66%) children participated in the questionnaire study. We may argue about how fearful the non-participating parents would have been. They may either have been relatively more afraid, and therefore have not participated, or less afraid and therefore have considered it not necessary to participate in the randomised controlled trial and the questionnaire study. Therefore, it is justified to discuss the results of the questionnaire study with respect to parents of children with recurrent febrile seizures.

The present questionnaire study population is different compared to studies that have addressed similar issues in questioning parents whose child had just suffered its initial febrile seizure[10-12]; only one study questioned also parents later on, until 20 months after the initial seizure[11] and one other included only parents who had witnessed the seizure.[10] In a recent study among parents of children with febrile seizures 40% reported full relief compared to what they had felt at the time of the acute event owing to reassuring information provided by the hospital after the seizure had occurred.[13] The parents of all these previous studies had not participated in a preventive trial and may have been provided reassuring information only once. Thus, the parents in the present questionnaire study may be considered relatively experienced, compared to the parents participating in the other studies: they have participated in a randomised controlled trial to prevent recurrences, implying that they have been repeatedly provided with reassuring information regarding fever and febrile seizures and their child has likely suffered from recurrent seizures; they might have become used to it. Thus, it is surprising that they are afraid of fever and seizure recurrence at a level not clearly different compared to the other studies.[10-13] We might have expected that the information repeatedly provided would have reduced their fear, but clearly it has not completely countervailed their fear.

The parents in the present questionnaire study had no clear misconceptions about what they defined as high fever or how high fever could rise if untreated, which is in contrast with parents who were not educated about fever.[1,2] Furthermore, 21% of the parents mentioned the information provided as their reason for considering febrile seizures not harmful. Thus, in the 'general population', parents with a child affected by febrile seizures may be even more frightened about fever and febrile seizures, because they probably have received less information.

Parental fear includes several negative consequences: fearful parents frequently repeat rectal temperature measurements, which is not beneficiary to the child: 25% measures five times or more during fever. Furthermore, 24% sleeps in the same room as the child or stays up all night (13%), to be alarmed in time if a febrile seizure might occur. These measures certainly have negative implications for daily family life. Parents' restless sleep is a major problem, which is even worsening with the frequency of febrile seizures recurrences in their child.[11] The consequences of being frightened by a febrile seizure are expensive and redundant: at the initial febrile seizure of their child, 55% of the parents call the national emergency number for an ambulance.[12] Other parents drive by car to the hospital (16%), which is a stressful and dangerous event with a child of whom they think is dying. The best thing to do is contact the general practitioner for further advice. In our study, 24% of the parents called or visited a general practitioner at the initial seizure affecting their child. Although this is a substantial percentage of adequate acting, we should try to increase this number in future parents.

The fact that parents think their child is dying, in our study in 47% at the initial febrile seizure, indicates a lack of information. The prevalence of febrile seizures is 4%[14]; since they are so commonly occurring, it would seem useful to provide more information about febrile seizures.[10-13] If parents receive information before the first seizure of their child occurs, a substantial number of them may remember the information and recognise a febrile seizure, which will reduce the fear and increase adequate acting.[11] The efficacy of health education to parents may be illustrated by the improvement of parental confidence after education about fever, demonstrated by a subsequent decrease in emergency hospital visits because of fever affecting their child.[15] Negative effects of providing information may entail increasing fear of fever; the fact that something so strange and frightening as a seizure may happen to the child during fever may induce an increase in parental fear and medical consumption of parents, who otherwise would not have contacted their general practitioner or the hospital. Balancing qualitatively the positive and negative effects, we advocate providing information to any parent when they visit the primary health care centre. The relatively high prevalence and the substantial parental fear, may be the strongest motive for febrile seizures to provide information about in primary health care centres.

In the present questionnaire study the parents' major source of information was the hospital (64%), likely due to several hospital visits and participation in the febrile seizures trial; the first line health care and the child health centres provided information to just a minority of these parents (10%). In the Netherlands, generally more than half of all children affected by febrile seizures will never visit a hospital after a febrile seizure.[16] Therefore, the preventive care and first line health care providers may be considered a major source of information regarding fever and febrile seizures.

Furthermore, general practitioners and pediatricians may be unaware of the stresses that parents of children with febrile seizures experience.[10,11] The results of our study show that parental fear is a substantial problem: 44% of the parents said to be afraid of recurrent seizures affecting their child again. The parents' fear should be discussed after the initial febrile seizure. Specific information is needed by parents who have watched their child during a febrile seizure to avoid long term adverse reactions.[11] We have demonstrated that specifically mothers with a low level profession and parents of children with a non-West European background and a multiple type initial seizure need extra attention regarding their fear. They

will benefit from information about the benign prognosis of febrile seizures. In non-West European parents, cultural differences regarding feverish diseases may play a role in understanding the information provided. Further, from the fact that all participating parents had to be Dutch or English speaking, we may derive that this does not exclude the possibility of subtle linguistic distinctions as a complicating factor in the communication. These issues require specific attention.

Conclusions

At least half of the parents of children affected by febrile seizures is afraid of fever, because they are afraid of febrile seizures. Parents fear' implies substantial negative consequences for daily family life. Adequate provision of information may reduce parental fear. Extra attention is necessary for the parents of children with a non-West European origin.

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4

Prevention of recurrence

4 Randomized controlled trial of ibuprofen to prevent febrile seizure recurrences

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Summary

Objectives Febrile seizures frequently recur. In daily practice, children with febrile seizures are often treated with antipyretics during fever to prevent febrile seizure recurrences. So far, no randomized placebo controlled trial has been performed to assess the efficacy of intermittent antipyretic treatment in the prevention of seizure recurrence.
Methods We performed a randomized double blind placebo controlled trial, in which 230 children, aged 1-4 years, with risk factors for febrile seizure recurrence, were enrolled. They were randomly assigned to either ibuprofen syrup, 20 mg per ml, 0.25 ml (=5 mg) per kg body weight per dose (111 children) or matching placebo (119 children), to be administered every six hours during fever (temperature ≥ 38.5°C). The primary outcome was the first recurrence of a febrile seizure. Kaplan-Meier curves and Cox regression were used for the statistical analysis.
Results Median follow up time (25-75 percentiles) was 1.04 years (0.7-1.8 years) in the ibuprofen group and 0.98 years (0.7-1.6 years) in the placebo group. The two-year recurrence probabilities were 32% and 39%, respectively (p=0.70). The recurrence risk in the ibuprofen group was 0.9 (0.6-1.5) times the recurrence risk in the placebo group ('intention-to-treat'). Adjustment for baseline characteristics did not affect the risk reduction estimate. A 'per-protocol' analysis showed similar results.
Conclusion We found no evidence that ibuprofen administration during fever prevents febrile seizure recurrence.

Introduction

Febrile seizures are the most common type of seizures in childhood, with a cumulative incidence of 4%[1] and an average recurrence risk of 30% in two years. Factors increasing the risk of febrile seizure recurrences include young age at onset, family history of febrile seizures, previous recurrent febrile seizures, time lapse since previous seizure less than six months, temperature lower than 40.0 °C at the initial febrile seizure, multiple type initial febrile seizure and frequent febrile illnesses.[2-8]

In recent years, the prevention of recurrent febrile seizures has become a debatable issue: prevention may not be necessary because almost all febrile seizures are not injurious to the child.[9-11] However, prevention of seizure recurrences serves two useful purposes: meeting parental fear of recurrent febrile seizures in general[12,13] and reducing the (small) risk of a long lasting and eventually injurious recurrent seizure.[9-11]
Intermittent treatment with diazepam during fever is associated with adverse effects and has not been proven efficacious to prevent febrile seizure recurrences.[14] Intermittent treatment of the child with antipyretic drugs is likely to be a rational alternative. Although children with febrile seizures are often treated with antipyretics in daily practice, until now no proper evaluation of the efficacy of antipyretic treatment in comparison with placebo to prevent febrile seizure recurrences has been carried out.[15-17] The aim of this study is to assess the efficacy of ibuprofen to prevent febrile seizure recurrence in children with an increased risk for recurrence.

Patients and Methods

Patients

Children who were seen for a febrile seizure at the Sophia Children's Hospital in Rotterdam and the Juliana Children's Hospital in The Hague, The Netherlands, between April 1, 1994 and April 1, 1996 were considered for inclusion. These hospitals have pediatric emergency wards which are open twenty-four hours per day.

A febrile seizure was defined according to the NIH consensus as 'an event in infancy or childhood, associated with fever but without evidence of intracranial infection or defined cause'.[18] Criteria for inclusion were: febrile seizure within the last six months, between one and four years of age; and presence of one or more risk factors for febrile seizure recurrence. Risk factors were defined as: a positive first degree family history of febrile seizures; an initial febrile seizure of the multiple type; a temperature below 40.0 °C at the initial febrile seizure; and previous febrile seizure recurrence(s). All parents had to give written informed consent for participation of their child in the study. Criteria for exclusion were: previous seizures without fever; known allergy for ibuprofen; current use of anti-epileptic drugs; no telephone connection; non-Dutch and non-English speaking parents.
The study protocol was approved by the ethical review boards of both institutions.

Study medication

Study medication consisted of either ibuprofen syrup, 20 mg per ml, 0.25 ml (=5 mg) per kg body weight per six-hourly dose, or matching placebo, to be given by the parents during fever. Parents were instructed to take the rectal temperature of the child immediately when the child seemed ill or feverish, and to start promptly with administering of study medication when the temperature was 38.5 °C or higher. Each dose was to be administered every six hours until the child was afebrile for twenty-four hours. The parents were instructed not to administer any other antipyretic drug to their child.

According to a computer generated randomization schedule, which was stratified by center, each child was assigned at study entry to either the ibuprofen or to the placebo arm of the

study. Only the biostatistician and the hospital pharmacists knew the actual treatment allocation.

Procedures

Baseline characteristics, including demographic characteristics, characteristics of the initial seizure and previous seizure recurrences, were recorded at study entry. Parents were instructed to record the precise timing of administering of the study medication and the height of the temperature in a standardized patient form. For measuring rectal temperature, a digital thermometer (Philips HP5316) was distributed. On the first day of fever onset, the child visited the outpatient clinic for assessment of the clinical condition, rectal temperature, compliance to the study protocol and registration of concomitant therapy. No laboratory tests were done, unless indicated by the clinical condition of the child. Antibiotic treatment was prescribed, if necessary. During subsequent treatment of the fever episode, parents had to call the investigator at least once per day. They had to notify the investigator in case of a febrile seizure recurrence. The investigator could be contacted by the parents twenty-four hours per day. If no fever had been reported after three months, the investigator contacted the parents to assure participation and to check the occurrence of fever or febrile seizure recurrence. Also, parents were instructed every three months about the dose of study medication to be used in order to account for bodyweight gain.

Statistical analysis

The outcome was the first recurrent febrile seizure. Follow-up time 'at risk' for this event was considered as terminated at the planned date of study termination (i.e. October 1, 1996), or when: any seizure (i.e. febrile or non-febrile) had occurred; the patient had left the out-patient clinic follow-up; further participation was refused; any medical condition occurred that precluded use of study medication to treat a fever episode. The cumulative probability over time 'at risk' of a first febrile seizure recurrence was estimated using the Kaplan-Meier method.[19] The two study medication groups were compared by Cox proportional hazards analysis,[20] using study medication allocation as the only covariate. Risk reduction by ibuprofen relative to placebo with its 95% confidence interval (CI95%) was estimated from the Cox model. Next, Cox proportional hazards modeling was used to assess whether correction for differences in baseline characteristics between the two study medication groups influenced the result.

Two analyses were performed. In an 'intention-to-treat' analysis, all first recurrent febrile seizures over the follow-up time 'at risk' defined earlier were considered, irrespective of study medication compliance by the parents of the child. A 'per-protocol' analysis was limited to those febrile seizure recurrences which occurred in the context of study medication compliance, defined as administration of study medication during an episode of fever according to the protocol before any febrile seizure recurrence had occurred. The definition of follow-up time 'at risk' was the same in both analyses.

The treatment effect on the temperature at 6 (±2) hours from fever onset was assessed using analysis of covariance, with temperature at fever onset as covariate.[21] Analysis of covariance was also used to assess the difference between temperature at seizure recurrence and temperature at fever onset and to assess the treatment effect on the temperature at seizure recurrence. Calculations were performed with SPSS for Windows, version 6.0.[22]

Power calculation

The two-year probability of seizure recurrence was assumed to be 40% in the placebo group. This relatively high figure was assumed because of the inclusion criterion of having at least one risk factor for febrile seizure recurrence. The required power was set at 80% (β=0.20) to detect a halving of the recurrence risk by ibuprofen (hazard ratio 0.5) with a type I error (α) of 0.05. Using the Egret Size package the required sample size was found to be 220 (110 in each study medication group).[23]

Results

Study population and protocol compliance

In total 478 children were considered for inclusion. Between October 1, 1994 and April 1, 1996, 230 of these were randomized (Figure 4.1); 111 to the use of ibuprofen and 119 to the use of placebo to treat any fever episode that might occur. Baseline characteristics are given in Table 4.1. The median follow-up time was 1.04 years (25 - 75 percentiles: 0.7-1.8 years) for ibuprofen and 0.98 years (0.7-1.6 years) for placebo.

Table 4.1 Baseline characteristics by treatment group

	ibuprofen n=111 (100%)	**placebo** n=119 (100%)
Demographic characteristics		
Female gender	41 (37%)	49 (41%)
Age at study entry[a]	1.9 (1.4-2.4)	1.9 (1.4-2.7)
First degree family history of febrile seizures	27 (24%)	32 (27%)
Family history of any seizures	44 (40%)	49 (41%)
Daycare attendance	39 (35%)	49 (41%)
First born	70 (63%)	59 (50%)
Caucasian origin	67 (60%)	78 (66%)
Immunization completed[b]	85 (77%)	88 (74%)
Initial seizure characteristics		
Age at onset[a]		
FSE[c]	1.4 (1.1-1.9)	1.5 (1.0-2.1)
Focal type[d]	8 (7%)	12 (10%)
Multiple type[e]	16 (14%)	10 (8%)
Rectal temperature below 40.0°C	47 (42%)	40 (34%)
Previous recurrent febrile seizures	55 (50%)	66 (56%)
Previous recurrent febrile seizures		
Time lapse between last seizure and study entry *	39 (35%)	45 (38%)
Number of risk factors	0.10 (0.05-0.21)	0.07 (0.04-0.18)
1	66 (60%)	66 (56%)
2	33 (30%)	44 (37%)
≥3	12 (11%)	9 (8%)

[a] in years, median (25th-75th percentiles)

[b] according to the national guidelines for immunization in the Netherlands

[c] febrile status epilepticus (FSE): seizure duration 30 minutes or more

[d] focal onset of the seizure or postictal Todd's paresis

[e] seizure recurrence within 24 hours

Characteristics printed in italics are the four risk factors for febrile seizure recurrence mentioned in the 'Patients' section

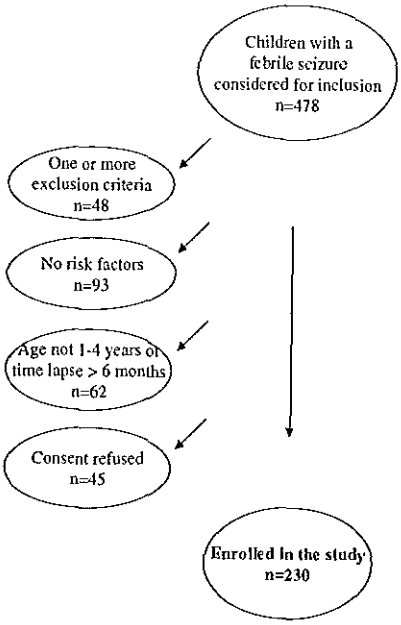

Figure 4.1 Recruitment of the study participants

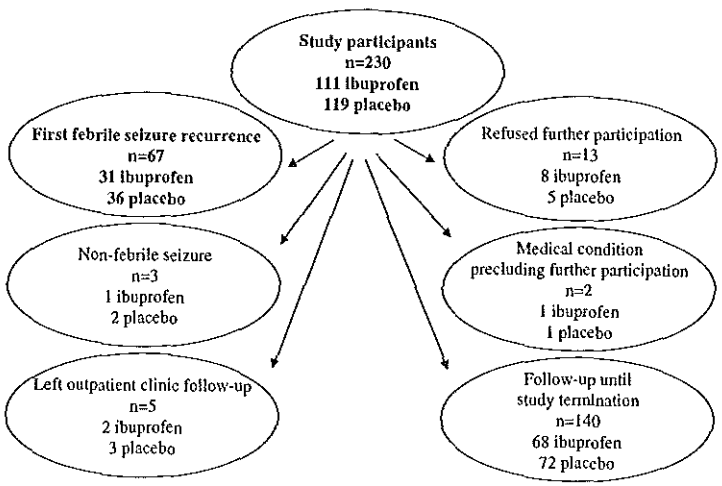

Figure 4.2 Events terminating follow-up time 'at risk'

Reasons for termination of follow-up are shown in Figure 4.2: 67 children had a first febrile seizure recurrence.

During follow-up, 555 fever episodes were reported in 194 children distributed as follows over the treatment groups: 94 children allocated to ibuprofen (85% of 111) had a total of 271 fever episodes; 100 children allocated to placebo (84% of 119) had a total of 284 fever episodes. Table 4.2 shows that in 377 of all 555 fever episodes (68%), study medication was administered according to the protocol. Also the reported use of concomitant medication is given.

In 67 children (31 ibuprofen, 36 placebo; Figure 4.2), a first recurrent febrile seizure occurred during a fever episode. In the 'intention-to-treat' analysis, these 67 children were considered as having reached the outcome studied. Of these, 30 first febrile seizure recurrences occurred in the context of study medication compliance (13 ibuprofen, 17 placebo). The 'per-protocol' analysis was limited to these events.

Effect of ibuprofen on febrile seizure recurrence

The cumulative probability over time of a first febrile seizure recurrence by treatment group as estimated by the Kaplan-Meier method based on 'intention-to-treat' (i.e. 31 events on ibuprofen, 36 on placebo) is shown in Figure 3. The two-year estimated recurrence probability was 32% for ibuprofen and 39% for placebo (p = 0.70). The recurrence risk in the ibuprofen group was 0.9 times the recurrence risk in the placebo group (CI95%: 0.6-1.5). The risk reduction estimate was similar when the analysis was adjusted for baseline characteristics. A 'per-protocol' analysis (i.e. using the 13 events on ibuprofen and 17 on placebo for which study medication was used) showed similar results (risk reduction 0.8, CI95%: 0.4-1.7).

Table 4.2 Compliance and concomitant medication per fever episode by treatment group

	ibuprofen n=271 (100%)	placebo n=284 (100%)
Fever episodes without febrile seizure recurrence:		
Fully compliant	164 (61%)	183 (64%)
Not fully compliant		
Parents did not give the study medication and did not timely report fever	17 (6%)	6 (2%)
Parents deviated from the prescribed dose	54 (20%)	56 (20%)
-and gave additional acetaminophen	4 (1%)	3 (1%)
-and gave diazepam rectal solution[a]	1 (<1%)	-
Fever episodes with febrile seizure recurrence:		
Fully compliant	13 (5%)	17 (6%)
Not fully compliant		
Parents did not give the study medication, because fever was not recognized previously to the seizure	11 (4%)	11 (4%)
Parents did not give the study medication, because of other reasons	7 (3%)	8 (3%)

[a] of the parents' own accord to prevent febrile seizure recurrence

Antibiotic treatment for suspected bacterial infection of the respiratory tract was prescribed to 8 children (1 in the ibuprofen group and 7 in the placebo group); 2 children received continuous antibiotic prophylaxis because of pre-existing vesico-ureteral reflux (1 in the ibuprofen group versus 1 in the placebo group).

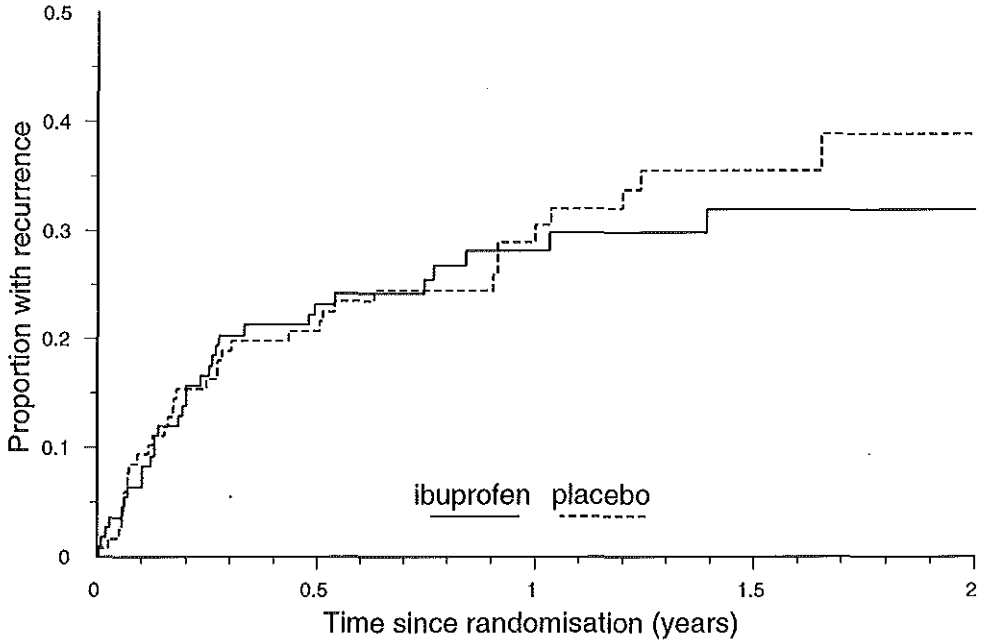

Figure 4.3 Cumulative probability over time of a first febrile seizure recurrence by treatment group ('intention-to-treat')

Temperature

Table 4.3 shows that the median temperature at fever onset was similar in both treatment groups. A significant reduction of the temperature at 6 (±2) hours after fever onset in the ibuprofen group compared to the placebo group was demonstrated, if all 555 fever episodes were considered (0.7 °C, $p<0.001$). In the fever episodes with a first febrile seizure recurrence, a temperature increase from fever onset until seizure recurrence was shown ($p<0.001$); the increase was not significantly different in the ibuprofen group compared to the placebo group, neither in the intention-to-treat analysis nor in the per-protocol analysis (in both analyses $p>0.20$).

Discussion

The present study failed to demonstrate a preventive effect of intermittent antipyretic treatment with ibuprofen during fever on the number of febrile seizure recurrences in children with an increased recurrence risk. The possibility of antipyretic treatment to reduce the risk of febrile seizure recurrence has been addressed before.[15-17] Table 4.4 summarizes the characteristics
of these studies. None were placebo controlled trials with a standardized antipyretic treatment schedule; hence, it is difficult to draw conclusions from these studies, with respect to the

Table 4.3 Temperature by treatment group

	ibuprofen group	placebo group
All fever episodes:	271	284
At fever onset	39.1 (38.7-39.4)	39.0 (38.7-39.3)
At 6(±2) hours after fever onset	38.2 (37.3-39.0)	38.9 (38.2-39.3)
Fever episodes with recurrence:		
Intention-to-treat analysis	31	36
At fever onset	39.0 (38.7-39.7)	39.4 (38.8-39.7)
At febrile seizure recurrence	39.9 (39.0-40.3)	39.6 (39.1-40.0)
Per-protocol analysis	13	17
At fever onset	39.0 (38.6-39.1)	39.5 (38.7-39.8)
At febrile seizure recurrence	40.1 (39.9-40.4)	40.0 (39.4-40.3)

Median temperatures in °C (25th-75th percentiles)

efficacy of antipyretic treatment to prevent febrile seizure recurrence. As the present study is the first placebo controlled trial of antipyretics to prevent febrile seizure recurrences, one can not be completely convinced that ibuprofen does not make a difference. The results, however, indicate that it is unlikely that intermittent antipyretic treatment reduces the number of febrile seizure recurrences.

We considered ibuprofen to be a promising drug to reduce the risk of febrile seizure recurrence. Both ibuprofen and acetaminophen administered orally have shown to be safe and effective antipyretic drugs in children with fever.[24-26] Because in these studies children with febrile seizures were excluded, we assessed the antipyretic efficacy of ibuprofen syrup, 5 mg per kg per six-hourly dose, versus acetaminophen syrup, 10 mg per kg per six-hourly dose, during fever in children with febrile seizures in a previous study.[27] The results indicated that antipyretics administered orally reduce fever in children with febrile seizures safely. In the first hours after the initial dose, ibuprofen showed a stronger temperature reducing effect compared to acetaminophen. We used a similar six-hourly dose of ibuprofen of 5 mg per kg in the present study. We confirmed the temperature reducing effect of ibuprofen at six hours after administering of the first dose, when the second dose was to be administered. The temperature lowering effect of ibuprofen could not be demonstrated in those fever episodes in which a recurrent febrile seizure occurred, neither in the intention-to-treat analysis, nor in the per-protocol analysis (Table 4.3). Some factors might have played a role in the reported inability of ibuprofen to reduce fever in those fever episodes.
The timing of temperature measurement was unfavorable to demonstrate the maximum antipyretic efficacy of ibuprofen; if the temperature had been measured earlier, we might have found a stronger antipyretic effect.[27] However, for the convenience of the study participants and their parents, the temperature measurements were not taken more frequently than every six hours, when the next dose of the study medication was administered.

Further, the parents may have taken the temperature under some stress due to their fear of a recurrent seizure resulting in a less than optimal reliability of the measurements. Since this has probably occurred equally in the ibuprofen group and the placebo group it is unlikely that the reported inability of ibuprofen to reduce fever in those fever episodes with a recurrence is due to unreliable measurements.

While discussing factors influencing both the inability of the present study to show fever reduction and prevention of seizure recurrences by ibuprofen, non-compliance of the parents of the child to the study protocol and unreported additional use of antipyretics should also be addressed. Compliance was ensured by using a standardized patient form in which administration of the study medication had to be written down by the parents. We neither used any marker of medication nor performed measurement of ibuprofen and acetaminophen blood levels to assess the compliance. The analysis of the temperature measurements in the total study group showed a clinically relevant and statistically significant temperature reduction in the ibuprofen group. Therefore, substantial compliance failures and unreported use of antipyretics are rather unlikely the cause of the inability of our study to show temperature reduction in those fever episodes in which a recurrence occurred and are also unlikely the cause of the inability of the study to show preventive efficacy on seizure recurrences.

If adequate reduction of fever prevents seizure recurrences, prevention may only be possible with the use of a much stronger temperature reducing agent, such as a higher dose of ibuprofen or other temperature reducing methods. For instance a dose of 10 mg ibuprofen per kg might be administered, which is twice the dose we have used, and which has been recommended in children with high fever. It is unknown, however, whether stronger fever reducing methods are able to lower the temperature in children with febrile seizures sufficiently to prevent febrile seizure recurrences.
In addition, specific conditions may affect the child's susceptibility to febrile seizure recurrence, such as conditions determined by the underlying cause of the feverish illness. The underlying cause of the fever may either be responsible for antipyretic treatment to fail in lowering the body temperature and therefore being ineffective to prevent seizure recurrences, or may provoke a febrile seizure, regardless of resistance to any fever reducing treatment.

In the present study, the 'per-protocol' analyses showed similar results as the 'intention-to-treat' analyses. Thus, a strong preventive efficacy of ibuprofen is unlikely, even when it has been administered in compliance with the study protocol. Nevertheless, it should be made clear that even if ibuprofen would be effective, then recurrences would occur frequently before an upcoming feverish illness is recognized. This is a problem inherent to any intermittent preventive treatment of febrile seizure recurrences, because it reduces the preventive efficacy. We found a recurrent febrile seizure as the presenting sign of fever in 22 (33%) of all 67 recurrences (Table 4.2). Likewise, in a study comparing intermittent diazepam administered rectally during fever and no preventive treatment, the fever was not recognized previously to 7 (33%) of the 21 recurrences in the intermittent diazepam group.[28] In another study of oral intermittent diazepam versus placebo, the seizure was the first manifestation of

Table 4.4 Previous randomised controlled studies of prevention of febrile seizure recurrences including antipyretic treatment

	Camfield, 1980
Treatment groups (number of children)	single daily dose of phenobarbital per os 5 mg/kg plus antipyretic instruction of the parents (n=39) versus antipyretic instruction including oral antipyretics only (n=40)
Temperature measurements	oral and rectal measurements by the parents at home
Outcome measure	first febrile seizure recurrence in the same or following fever episodes
Maximum study duration	12 months
Patient inclusion	simple initial febrile seizure
Major difficulties in the evaluation of the results	-no standardization of the antipyretic treatment[a] -no placebo control group of antipyretic treatment
Results	2 of the 39 patients using phenobarbital plus anti-pyretic instruction and 10 of the 40 patients with only instruction had a recurrent febrile seizure[c]
Efficacy of antipyretic preventive	not effective

[a] all parents received instructions about fever control; no standardized dosis per kg bodyweight was administered
[b] all parents were allowed to administer extra antipyretics, whenever they believed they should
[c] survival analysis was performed to compare seizure recurrence in the phenobarbital plus instruction group and the instruction only group ($p<0.02$, log-rank)
[d] survival analysis was performed to compare seizure recurrence in the diazepam group and the placebo group ($p=0.41$, log-rank)

fever in 42%(14/33) of all seizure recurrences.[29] In a study comparing diazepam with valproic acid, both administered rectally during fever only, there were no signals of an upcoming feverish illness in 31% (11/36) in all seizure recurrences.[30] In a study comparing oral diazepam with placebo during fever, 60% (68/113) febrile seizure recurrences occurred without the child receiving the study medication, in part because the seizure was the first sign of illness.[31]

Until the recent past, children with recurrent febrile seizures were used to be treated by continuous antiepileptic drugs to prevent further recurrences. Because of the severity of negative side effects and the debatable efficacy, continuous antiepileptic treatment of children with febrile seizures nowadays is considered obsolete in general, unless there are strong indications.[14] Accordingly, intermittent preventive treatment with diazepam during fever is associated with adverse effects and has not shown to be effective in a meta-analysis[14]; exclusively children with a high risk of febrile seizure recurrence may benefit from

Schnaiderman, 1993	Uhari, 1995
prophylaxis of acetaminophen orally 15-20 mg/kg per 4-hourly dose (n=53) versus sporadic usage of acetaminophen of a similar oral dose contingent at fever above 37.9 °C (n=51)	diazepam 0.2 mg/kg 8-hourly during fever above 38.5 °C (n=81), of which the first dose to be given rectally and further doses per os, versus placebo (n=80); additional: cross-over per fever episode with acetaminophen 10 mg/kg 6-hourly during fever above 40.0 °C (route of administration not reported) versus placebo
rectal measurements by nurses or parents during hospitalization	(oral or rectal) measurements by the parents at home
-first febrile seizure recurrence in the same fever episode (multiple type) -body temperature	-number of febrile seizure recurrences in any of the following fever episodes -body temperature
one fever episode	two years
simple initial febrile seizure	simple or complex initial febrile seizure
-no placebo control group of antipyretic treatment -non-comparable outcome measure	-no standardization of the antipyretic treatment[b]
4 of the 53 children using ongoing prophylaxis versus 5 of the 51 children in the sporadic usage group had a recurrent seizure in the same fever episode	9 of the 173 fever episodes were associated with a recurrence in the acetaminophen group versus 14 of the 170 fever episodes in the placebo group[d]
not effective	not effective

intermittent diazepam in an oral dose of 0.33 mg per kg to be administered every eight hours during fever.[31] The decision to prescribe it should be made in consultation with the parents, because of its negative side effects, the necessity of regular medical check ups and the difficulty of early recognition of a feverish illness. Negative consequences of focusing on prevention of seizure recurrence may entail an iatrogenous fear of the parents unwittingly encouraged by the pediatrician.[32] Probably the most important issue in treating children with febrile seizures is to make efforts to reduce parental anxiety by providing information about the excellent prognosis of febrile seizures.[9-11,33]

We conclude there is no evidence supporting intermittent antipyretic treatment to prevent febrile seizure recurrences. Antipyretics may be given during a febrile illness, with the aim to make the child feel more comfortable. Consultation with the parents should emphasize the generally benign character of febrile seizures.

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5

Prediction of recurrence

5.1 The frequency of fever episodes related to febrile seizure recurrence

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Summary

Objective To assess the number of fever episodes as a risk factor for febrile seizure recurrence during the first six months after the last previous febrile seizure.
Methods Six months follow-up study of 155 children, aged 3 months to 5 years, with a first or a recurrent febrile seizure. The occurrence of fever episodes and febrile seizure recurrences was prospectively documented. With logistic regression analysis we studied the association between the baseline characteristics and the number of fever episodes and the outcome: a febrile seizure recurrence.
Results We registered 260 fever episodes. 29 children experienced one or more febrile seizure recurrences during follow-up. We identified two factors associated with febrile seizure recurrence: number of fever episodes (OR=1.8 (CI95%: 1.4-2.4)) and age at study entry (OR=0.6 (CI95%: 0.3-1.1)). In a multivariable model, only the number of fever episodes remained significant.
Conclusion The number of fever episodes increases the risk of a febrile seizure recurrence with a factor 1.8 per fever episode in the first six months after a febrile seizure.

Introduction

With a cumulative incidence of 4%, febrile seizures are the most common type of seizures in children aged three months to five years.[1,2] The two-years probability of a febrile seizure recurrence has been estimated as 30% on average; 10 to 20% of the seizures recur within six months, with a decreasing risk after the first six months following the previous seizure.[3,4]
The risk of febrile seizure recurrences has been studied rather thoroughly.[3-9] The major and most consistent risk factors are: young age at onset, family history of febrile seizures, previous recurrent febrile seizures, a low temperature at the initial febrile seizure, a multiple type initial febrile seizure and short time lapse since the previous seizure.

Additionally, it has been demonstrated that frequent fever episodes are associated with an increased recurrence risk.[9,10] Children have the highest recurrence risk in the first six months after the last previous febrile seizure. We aimed to assess the incidence of fever episodes in relation with febrile seizure recurrence in this high risk period for febrile seizure recurrence.

Patients and Methods

Patients

Children aged 3 months to 5 years, who were seen for an initial or a recurrent febrile seizure at the Sophia Children's Hospital in Rotterdam and the Juliana Children's Hospital in The Hague between April 1, 1994 and July 1, 1997 were considered for inclusion. Both outpatients' clinics include mainly basic specialist care. Eligible children were either enrolled in a randomised placebo-controlled trial of ibuprofen syrup to prevent febrile seizure recurrences (1994-1996), of which the results will be reported elsewhere, or in a cohort study, in which the occurrence of fever episodes and febrile seizure recurrence during six months were registered (1996-1997). We adopted the definition of febrile seizure of the National Institutes of Health Consensus Meeting.[2] The parents of all participating children gave their written informed consent. The study protocol was approved by the relevant local ethical review boards.

Additional inclusion criteria for the children in the randomised controlled trial were: aged between 1 and 4 years, presence of one or more risk factors for seizure recurrence, defined as: a positive first degree family history of febrile seizures; an initial seizure of the multiple type; a temperature below 40 °C at the initial febrile seizure; and one or more previous febrile seizure recurrences.

Exclusion criteria for the present study were: more than two months time lapse between the last previous febrile seizure and study entry; current use of anti-epileptic drugs; no telephone connection; non-Dutch and non-English speaking parents. Of the randomised controlled trial we included the children who were allocated to placebo only.

Methods

After the children had visited the emergency room of the hospital with a febrile seizure, they received an appointment for special febrile seizure outpatients' clinic hours, where they were examined and the parents were provided information regarding fever and febrile seizures. The parents were advised against giving their child antipyretics during fever.

Baseline characteristics were recorded and checked at study entry, including age, gender, family history of febrile seizures and epilepsy, date and characteristics of the initial febrile seizure, the number of previous recurrent febrile seizures and the date of the last previous febrile seizure. Of the initial febrile seizure, the temperature and the presence of complex characteristics were documented. Complex characteristics were defined as seizure duration of 15 minutes or more and/or recurrence of the seizure within 24 hours (multiple type) and/or a focal onset of the seizure or a postictal Todd paresis of facial muscles or limbs (focal characteristics).[11,12]

If parents consented to participate in the randomised controlled trial, they were instructed to take the rectal temperature of the child immediately when the child seemed ill or feverish and to start promptly with administering of study medication when the temperature was 38.5 °C or higher. They were instructed to record the precise timing of administering of the study medication and the height of the temperature in a standardised patient form. They had to notify the investigator of each fever episode and recurrent febrile seizure. If no fever had been

reported after three months, the investigator contacted the parents to assure participation and to check the occurrence of fever or febrile seizure recurrence. When a febrile seizure recurrence occurred, follow-up time was considered as terminated for the randomised trial; however, the parents were asked to continue to list all subsequent fever episodes and seizure recurrences until the planned date of study termination (October 1996).

Parents who consented to participate in the cohort study were provided six diaries. They were instructed to use subsequently one diary per month of follow-up to register the occurrence of fever episodes and recurrent febrile seizures. The parents were instructed to document every day whether or not their child was feverish. When the child seemed ill or feverish, the parents took the child's rectal temperature; when the rectal temperature was 38.5 °C or more, they were asked to mark that day with 'yes' and when the rectal temperature was lower than 38.5 °C, with 'no'. Accordingly, the occurrence of one or more febrile seizure recurrences was documented. After every month of follow-up, the parents sent the diary to the investigator. If the diary was not received promptly or if data were not filled in, the parents were contacted to assure participation and to check the occurrence of fever or febrile seizure recurrence.

Statistical analysis

The outcome was defined as the occurrence of a febrile seizure recurrence in six months follow-up time at risk. If follow-up time was terminated before six months, children were excluded from the analysis. Early termination of follow-up was defined as: development of afebrile seizures; starting the use of intermittent prophylactic diazepam; and refusal of further study participation.

We used logistic regression analysis to assess the association between baseline characteristics, the number of fever episodes and the outcome. Baseline characteristics included the following risk factors for febrile seizure recurrence: a first degree family history of febrile seizures, age at onset under one year, temperature at the initial febrile seizure below 40 °C, multiple type initial febrile seizure and one or more previous recurrent febrile seizures. All characteristics with $p<0.10$ in the univariable analysis were entered in a multivariable model, to adjust for their interrelation. Odds Ratios (OR) were used as measure of association. Associations were statistically significant ($p<0.05$), if the 95% confidence interval (CI95%) of the OR did not include the value one. SPSS for Windows was used for the analysis.

To assess any difference between the randomised controlled trial group and the cohort study group, we performed univariable regression analyses in both groups separately. If different OR's for baseline characteristics were found, a study-interaction term, indicating the original study (randomised controlled trial or cohort study), was introduced in the model and was multiplied with the baseline characteristics involved, to assess whether differences were likely due to chance.

Results

Study population

The study population consisted of 171 children; 89 (52%) children allocated to the use of placebo in the randomised controlled trial and 82 (48%) children in the cohort study. Sixteen children of the cohort study were excluded from the analysis, because of early termination. Of these, two children developed afebrile seizures, one child received intermittent prophylactic treatment with diazepam; and 13 parents refused after informed consent had initially been given. Thus, the data of 155 children were used for the analysis; 89 children from the randomised controlled trial and 66 children from the cohort study.

Febrile seizure recurrence during follow-up

Of all 155 children, 29 (19%) children had one or more febrile seizure recurrences and 126 (81%) had no febrile seizure recurrence during six months follow-up. Forty-one febrile seizures occurred; 20 children suffered one recurrence, 6 children had two recurrences and 3 children had three recurrences.

A total of 260 fever episodes was counted in 155 children; the mean number of fever episodes per child was 1.7. Of all 155 children, 42 (27%) had no fever episodes and 113 (73%) had one or more fever episodes. Among those 113, 29 children had a febrile seizure recurrence who had 89 fever episodes (mean number of fever episodes per child: 3.1, median 2.0). The 126 children without a recurrence had 171 fever episodes (mean: 1.4, median 1.0).

Table 5.1.1 Baseline characteristics, fever episodes and febrile seizure recurrence

	Recurrence		Univariable analysis		Multivariable analysis	
	Yes n=29 (100%)	No n=126 (100%)	OR(CI95%)	p-value	OR(CI95%)	p-value
Baseline characteristics						-
Female gender	13(45%)	43(34%)	1.6(0.7-3.6)	0.28	-	0.89
Age at study entry[a]	1.6(1.3-2.1)	1.8(1.42.6)	0.6(0.3-1.1)	0.09	1.0(0.5-1.8)	
Number of febrile episodes[b]	2.0(2.0-4.0)	1.0(0.0-2.0)	1.8(1.4-2.4)	<0.001	1.8(1.4-2.4)	<0.001

[a] median age and 25th-75th percentiles in years
[b] median and 25th-75th percentiles

As shown in Table 5.1.1, in the univariable analysis age at study entry (OR=0.6) and number of fever episodes (OR=1.8) were associated with febrile seizure recurrence (p<0.10). The other baseline characteristics, including the risk factors for febrile seizure recurrence, were not associated with febrile seizure recurrence. In a multivariable model, the number of febrile episodes was significantly associated with febrile seizure recurrence. The risk of a febrile seizure recurrence was increased with a factor of 1.8 per fever episode in the first six months after the last previous febrile seizure. Age at study entry had no additional effect on the outcome in the multivariable model (OR=1.0). Figure 5.1.1 illustrates that children at young age experienced more fever episodes. It can be read from this figure that children with a recurrence during follow-up experience more fever episodes. For a given number of fever

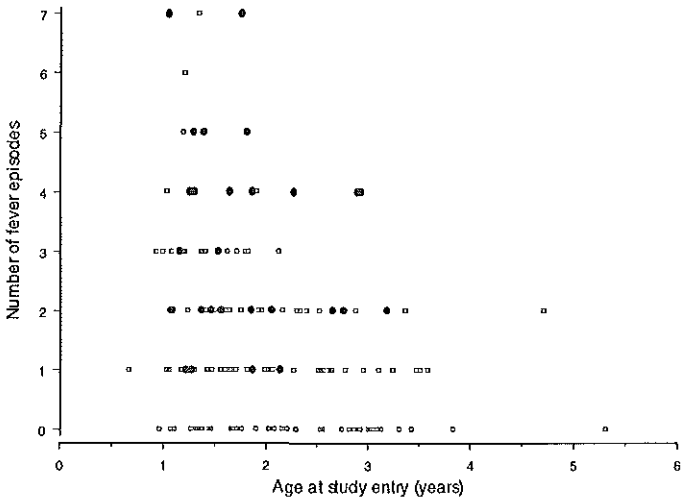

Figure 5.1.1 The number of fever episodes in relation to the age at study entry and febrile seizure recurrence. The open cubes show the cases without a febrile seizure recurrence during follow-up and the black dots represent the cases with a febrile seizure recurrence during follow-up.

episodes, the risk of recurrence shows no clear association with age. Children at young age have more recurrences due to the high number of fever episodes at young age.

In separate analyses of the randomised controlled trial and the cohort study, no statistically significant differences were found in the OR of baseline characteristics with febrile seizure recurrence. We also assessed the separate probabilities of febrile seizure recurrence in six months follow-up: 21% in the randomised controlled trial and 15% in the cohort study (χ^2, p=0.33).

Discussion

The present study demonstrates that the number of fever episodes was a factor independently associated with a febrile seizure recurrence in the first six months after the last previous febrile seizure. The risk of a febrile seizure recurrence was increased with a factor 1.8 per fever episode; children with febrile seizures who suffer frequently from feverish illnesses have a high recurrence risk. Two follow-up studies of children who had had an initial febrile seizure found similar results.[9,10] Rantala et al. evaluated retrospectively the frequency of fever episodes and febrile seizure recurrences, using a mailed questionnaire. After a mean follow-up period of 3.8 years, they found that the number of fever episodes was a significant risk factor for recurrence of febrile seizures. Unfortunately, no quantification of the relative risk was reported.[9] Knudsen et al. demonstrated that in the year after an initial febrile seizure, children who suffer few fever episodes (defined as less than four per year) had 0.06 times the risk of

febrile seizure recurrence of children suffering four or more fever episodes per year (OR 1:16).[10] Concordantly, when we categorised the number of fever episodes in our study (less than two episodes versus two or more episodes per six months) we found a comparable risk reduction of 0.09 in the group of children with less than two fever episodes per six months.

In the present study the mean number of fever episodes per child was 1.7 in six months follow-up. Children with one or more febrile seizure recurrences had a mean of 3.1 versus 1.4 in children who experienced no febrile seizure recurrence, illustrating a higher frequency of febrile episodes in children with febrile seizure recurrence. In other febrile seizure studies, the mean number of fever episodes per child per year has been reported as 3.0[10] or was calculated from the presented data as 1.5 to 1.9[9,13,14] All these studies had a median follow-up time longer than six months. The relatively high estimate of 1.7 fever episodes per six months in the present study is likely due to the fact that the risk over time may not be constant, since increasing age decreases the incidence (Figure 5.1.1).[10]

In the present study the combination of the data of the randomised controlled trial and the cohort study is justified, because both are prospective follow-up studies, which have been carried out in the same hospitals, by the same investigators, within a ongoing study period of three years (1994-1997). All parents had received similar instructions regarding the use of antipyretics and children had not received a standardised dose of ibuprofen during fever. All children had a similar follow-up time at risk of six months. Further analysis of the two original studies separately showed no difference with respect to association of baseline characteristics with febrile seizure recurrence.

We reported the six months probabilities of febrile seizure recurrence of both studies separately (21% and 15%, respectively). The fact that the children who had been participating in the randomised controlled trial had one or more risk factors at study entry may explain the slightly higher recurrence risk. Further, the recurrence risk of 15% per six months in the cohort study is in accordance with previous reported average probabilities of 10 to 20%.[3,4]

The association between the number of fever episodes and seizure recurrence may suggest that the factor 'chance' plays an important role in the pathophysiology of febrile seizures. The more fever episodes a child experiences, the higher will be the probability of another recurrent seizure, independent from other risk factors of febrile seizure recurrence.

Further, the results of the present study may have consequences for the provision of information to the parents. If their child usually suffers from frequent fever episodes, they may be acquainted of a probably increased risk of seizure recurrence in the first six months after a febrile seizure. If intermittent preventive treatment (i.e. diazepam during fever, 1 mg/kg body weight per day, given in three doses) is considered necessary, because of a very high recurrence risk or very frightened parents, the frequency of fever episodes may play a additional role in this decision.[14] However, parents may also be reassured because the number of fever episodes will decrease if their child grows older; thus, febrile seizure recurrence risk will decrease accordingly.

Conclusion

The number of fever episodes is independently associated with febrile seizure recurrence. During the first six months after a febrile seizure the recurrence risk is increased with a factor 1.8 per fever episode.

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5.2 Temperature, age and febrile seizure recurrence

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Summary

Objective Prediction of a recurrent febrile seizure during subsequent fever episodes.
Design We studied the data of the temperatures, seizure recurrences and baseline patient characteristics, that were collected at a randomized placebo controlled trial of ibuprofen syrup to prevent febrile seizure recurrences.
Setting Two pediatric hospitals in the Netherlands.
Patients 230 children with an increased risk of febrile seizure recurrence.
Main outcome measure Seizure recurrence during a subsequent fever episode.
Results We registered 509 fever episodes with 67 recurrences; 35 (52%) recurrences within the first two hours after fever onset had a lower median temperature (39.3 °C) than 32 (48%) after more than two hours of fever (40.0 °C, $p<0.001$).
Poisson regression analysis resulted in three univariably significant ($p<0.05$) predictors of a seizure recurrence during a subsequent fever episode. In a multivariable model, they were corrected for their correlation: time interval between the last previous seizure and fever onset less than six months (RR=1.3 (CI95%: 0.8-2.4)), age at fever onset (RR=0.7 (CI95%: 0.5-1.0) per year increase) and temperature at fever onset (RR=1.7 (CI95%: 1.1-2.8) per °C increase). Analysis of seizure recurrence per six hours time period of fever resulted in similar associations. If we included the temperature at onset of each six hours time interval, the prediction showed to be more accurate: a larger relative risk and smaller p-value.
Conclusion Half of the recurrent seizures occur in the first two hours after fever onset of a subsequent fever episode. If seizure recur at a later time, the temperature at seizure is higher compared to recurrences occurring in the first two hours of fever. Young age at fever onset, high temperature at fever onset, and high temperature during the fever episode are associated with an increased risk of a recurrent febrile seizure at the moment that a child with a history of febrile seizures has fever again.

Introduction

The last decade, several risk factors for seizure recurrence in children affected by febrile seizures have been defined. These include young age at onset, family history of febrile seizures, previous recurrent febrile seizures, time lapse since previous seizure less than 6 months, a low temperature (lower than 40.0 °C) at the initial febrile seizure and a multiple

type initial febrile seizure.[1-6] Furthermore, frequent fever episodes have shown to be associated with an increased risk of recurrent febrile seizures.[7,8] However, it is also of practical interest to predict a febrile seizure recurrence during subsequent fever episodes. To our knowledge, this has never been investigated before. A fever episode is, in fact, the only time that the child is at risk to suffer from a recurrent febrile seizure.[9] The body temperature during a fever episode has been reported to play a role in the development of a febrile seizure.[10,11] Further, seizure recurrence risk decreases with age[4,6] In this study we aim to clarify the effects of these and other previously reported risk factors for seizure recurrence. Therefore, we have examined the temperatures during fever and the baseline patient characteristics of 230 children with febrile seizures who participated in a randomized double blind placebo controlled trial of ibuprofen to prevent febrile seizure recurrences.[12] We report the analysis of factors that predict a seizure recurrence during subsequent fever episodes.

Patients and Methods

Patients

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

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

Procedures

According to the protocol, the parents were instructed to take the rectal temperature immediately when their child seemed ill or feverish and to start with administering of the study medication if the temperature exceeded 38.4 °C. In the present study this moment has been defined as fever onset. All temperatures were rectally measured with the Philips HP5316 thermometer. They were instructed not to administer any other antipyretic drug, to continue with administering the study medication and to measure the temperature every six hours until

the child was afebrile for 24 hours and to measure the temperature at seizure recurrence. If a child had a first febrile seizure recurrence after study entry, the study was stopped for that child and any subsequent fever episodes were not taken into account. At the first day of fever onset and after a recurrent febrile seizure, the child was physically examined. No laboratory tests were performed nor antibiotic treatment was started unless indicated by the clinical condition of the child.

Statistical analysis

The outcome was a febrile seizure recurrence during a subsequent fever episode.

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

Temperatures are given in median values, with their 25 and 75 percentiles between brackets. We used unpaired and paired non-parametrical tests to analyze differences in temperature at fever onset and at seizure recurrence.

For the analysis of seizure recurrence during subsequent fever episodes we used three types of data.

First, we analyzed the baseline characteristics known at study entry, including gender, age and the presence of the known risk factors for seizure recurrence as demonstrated by previous studies.[1,2,5,6]

Second, we considered patient characteristics that were unique for each fever episode: age at fever onset, the time interval between the last previous seizure and fever onset and the temperature at fever onset.

Third, the data of the temperatures that were measured every six hours during fever were used. This analysis considered seizure recurrence in each time period of six hours of fever, using the most up to date temperature data available.

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

We consider the Poisson model suitable, because we study a relatively rare event (=first febrile seizure recurrence) in a time interval which has a different duration for each individual patient and which consists of one or more separate time periods (=subsequent fever episodes). Univariable and multivariable Poisson regression analysis related patient characteristics to seizure recurrence. Associations were expressed as rate ratios, which we interpret as relative risks.[13] The level of statistical significance was set at 0.05. Calculations were performed with SPSS and EGRET.[14,15]

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

Results

Table 5.2.1 shows the patient characteristics at study entry of all 230 children. There were no clear differences in patient characteristics in the 182 (79%) children with at least one fever episode compared to the 48 (21%) children without a fever episode during follow up.

The parents reported 555 fever episodes. 46 (8%) of the fever episodes were excluded from the analysis, because the parents had not registered any of the temperature data during follow up. No recurrences occurred in these excluded fever episodes. We further analyzed the 509 fever episodes, in which 67 (13%) recurrences occurred. Thirty-five (52%) recurrences occurred within the first two hours after fever onset compared to 32 (48%) occurring after more than two hours of fever. The risk of a recurrence was 7% (35/509) in the first two hours after fever onset and 7% (32/(509-35)) after more than two hours of fever.

We analyzed the relation between the temperature and the first febrile seizure recurrence using all temperature measurements in the 509 fever episodes. The temperature at seizure recurrence was variably and relatively low (39.3 °C (39.0-39.8 °C)) in recurrences occurring in the first two hours compared to recurrences occurring after more than two hours of fever (40.0 °C (39.6-40.4 °C), $p<0.001$, Mann-Whitney U test).

Additionally, we analyzed all temperatures measured in the fever episodes in which a seizure recurrence occurred at two hours or more after fever onset (n=23 with complete temperature data). In those fever episodes the temperature at seizure recurrence (39.6 °C (39.1-40.1 °C)) was higher compared to the temperature at fever onset (39.3 °C (38.8-39.7 °C), $p<0.01$, paired Wilcoxon test).

Table 5.2.2 shows the results of the Poisson regression analysis of seizure recurrence per fever episode. Three univariably significant predictors were: time interval between the last previous seizure and fever onset, age at fever onset and temperature at fever onset. Age and temperature at fever onset had similar effects (RR=0.7) after adjustment for the correlation between these three characteristics; age at fever onset lost its statistical significance ($p=0.06$). The analysis was repeated using only the data of the fever episodes of the children randomized to placebo and showed similar results.

Table 5.2.1 Baseline patient characteristics of the study population at study entry (n=230)

	≥1 fever episode during follow-up n=182 (79%)	no fever episodes during follow-up n=48 (21%)	OR (CI95%)	p-value
Baseline characteristics:	71 (39%)	19 (40%)	1.0 (0.5-1.9)	0.94
Female gender *n=90 (39%)*	1.4 (1.0-1.9)	1.6 (1.2-2.2)	0.7 (0.5-1.1)	0.17
Age at initial seizure *1.4 (1.1-1.9)*[a]	44 (24%)	16 (33%)	0.6 (0.3-1.2)	0.17
First degree family history of febrile seizures *n=59 (26%)*				
Initial seizure characteristics:				
Temperature<40.0°C *n=121 (53%)*[b]	93 (51%)	28 (58%)	0.7 (0.4-1.4)	0.37
Multiple type *n=87 (38%)*	74 (41%)	13 (27%)	1.8 (0.9-3.7)	0.09
Recurrences before study entry[c]:				
0 recurrences *n=146 (64%)*	111 (61%)	35 (73%)	rc	-
1 recurrence *n=61 (27%)*	53 (29%)	8 (17%)	0.8 (0.5-1.2)	0.24
2 or more recurrences *n=23 (10%)*	18 (10%)	5 (10%)	1.6 (0.9-2.9)	0.15
Risk factors for recurrence[d]:				
1 or 2 risk factors *n=209 (91%)*	163 (90%)	46 (96%)	rc	-
3 or 4 risk factors *n=21 (9%)*	19 (10%)	2 (4%)	2.7 (0.6-11.9)	0.20
Age at study entry *1.9 (1.4-2.5)*[a]	1.9 (1.4-2.4)	1.9 (1.4-2.8)	0.8 (0.5-1.2)	0.31
Follow-up *0.8 (0.4-1.4)*[a]	0.8 (0.3-1.5)	0.7 (0.5-1.3)	1.1 (0.7-1.8)	0.76

[a] Median in years (25th-75th percentiles)
[b] Temperature measured at time closest to seizure time (documented in the emergency room or in the patient history)
[c] Initial seizure not counted as recurrence
[d] As described in the Patients section
rc reference category

Table 5.2.2 Patient characteristics and febrile seizure recurrence per fever episode (n=509)

	univariable analysis		multivariable analysis	
	RR (CI95%)	p-value	RR (CI95%)	p-value
Patient characteristics known at study entry				
Female gender	1.5 (0.9-2.5)	0.09		
First degree family history of febrile seizures	0.8 (0.4-1.4)	0.42		
Initial seizure characteristics:				
Temperature < 40.0 °C	1.1 (0.7-1.8)	0.65		
Multiple type	1.6 (1.0-2.5)	0.06		
One or more recurrences before study entry	0.9 (0.6-1.5)	0.76		
Number of risk factors for seizure recurrence	1.2 (0.9-1.7)	0.28		
Characteristics unique for each fever episode				
Time interval[a]:				
> 0.5 year	rc	-	rc	-
≤ 0.5 year	1.8 (1.1-2.9)	0.02	1.3 (0.8-2.4)	0.32
Age at fever onset (in years)	0.7 (0.5-0.9)	0.01	0.7 (0.5-1.0)	0.06
Temperature at fever onset (in °C)	1.7 (1.1-2.8)	0.02	1.7 (1.1-2.8)	0.02

[a] time period between last previous seizure and fever onset in years
rc reference category

Table 5.2.3 Patient characteristics and febrile seizure recurrence per six hours time period of fever (n=1931)

	univariable analysis	
	RR (CI95%)	p-value
Patient characteristics known at study entry		
Female gender	1.5 (0.1-1.5)	0.10
First degree family history of febrile seizures	0.8 (0.5-1.5)	0.54
Initial seizure characteristics:	1.1 (0.7-1.8)	0.69
Temperature < 40.0 °C	1.7 (1.1-2.8)	0.02
Multiple type	0.9 (0.5-1.5)	0.64
One or more recurrences before study entry	1.3 (0.9-1.7)	0.17
Number of risk factors for seizure recurrence		
Characteristics unique for each fever episode		
Time interval[a]:		
> 0.5 year	rc	
≤ 0.5 year	1.9 (1.1-3.1)	0.01
Age at fever onset (in years)	0.7 (0.5-0.9)	0.01
Temperature at fever onset (in °C)	2.0 (1.2-3.2)	0.01
Characteristics unique for each six hours time period of fever		
Temperature at onset of each six hours (in °C)	2.8 (2.0-3.9)	<0.001

[a] time period between last previous seizure and fever onset in years
[b] variables included in the multivariable model: time interval, age and temperature at fever onset
[c] variables included in the multivariable model: time interval, age at fever onset and temperature at onset of each six hours time interval of fever
rc reference category

Figure 5.2.1 shows the relation between age and temperature at fever onset versus the risk of a febrile seizure recurrence in the corresponding fever episode. The figure illustrates that the risk of a recurrence increases with temperature at fever onset and decreases with age. The lines indicate four arbitrarily chosen recurrence risks: 5%, 10%, 20% and 30%. For example, if the temperature at fever onset is 40.0 °C, a child aged one year has a 30% recurrence risk in the corresponding fever episode. This risk is between 5% and 10% for a 4-year-old child.

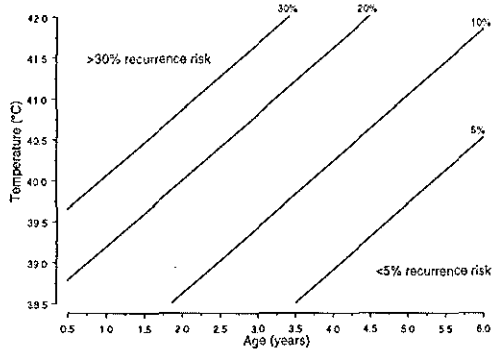

Figure 5.2.1 Relation between temperature at fever onset, age at fever onset and the risk of a febrile seizure recurrence per fever episode

multivariable analysis[b]		multivariable analysis[c]	
RR (CI95%)	p-value	RR (CI95%)	p-value
rc		rc	
1.4 (0.8-2.5)	0.28	1.9 (1.0-3.5)	0.04
0.7 (0.5-1.0)	0.05	0.8 (0.5-1.1)	0.19
2.0 (1.2-3.2)	0.01	-	-
-	-	2.9 (2.1-4.0)	<0.001

Table 5.2.3 shows the results of the Poisson regression of seizure recurrence per six hours time period of fever. The associations were similar to the associations in the model predicting seizure recurrence per fever episode (Table 5.2.2). In a multivariable analysis we included the three characteristics that were univariably significant in all analyses. If we included the temperature at onset of each six hours time period of fever, in stead of the temperature at fever onset, the multivariable relative risk was higher (2.9 versus 2.0) and the p-value smaller ($p<0.001$ versus $p=0.01$). The analysis using only the data of the children randomized to placebo gave similar results (RR=2.5(1.7-3.9), $p<0.0001$, for the temperature at onset of each six hours time period of fever).

Discussion

The present study shows that half of the febrile seizure recurrences during a subsequent fever episode occur within the first two hours of fever. Accordingly, other febrile seizure studies show that a substantial part of the seizure recurrences occur early in the fever episode and that febrile seizure recurrences are often the presenting symptom of a feverish illness.[16-18] However, previous studies have not demonstrated that the temperature at seizure recurrence in the first two hours after fever onset is clearly lower compared to the temperature at recurrences more than two hours after fever onset. These findings suggest a seizure provoking effect of either the temperature increase, or the high temperature level that has been reached. Furthermore, it might be that febrile seizures occurring after a short duration of fever are occurring in a different (more vulnerable) type of patients than seizures occurring later on. Follow up studies may give insight in the consistency of this pattern in the individual patient. At least, initial febrile seizures occurring after a short duration of fever are associated with an increased risk of recurrence.[4]

Age plays an important role in the susceptibility of febrile seizures; the risk of seizure recurrence declines with growing older.[1,2,6,19,20] If there is an individual temperature threshold level above which a febrile seizure will develop, this threshold is influenced by age: the older the child grows, the higher the threshold, the lower the risk. The results of our study are in accordance with these hypotheses and findings: age showed to be associated with a seizure recurrence, although in the multivariable model the level of statistical significance was not reached (p=0.06). Independently from either being longer at risk, or getting higher temperatures during fever, young age is associated with an increased recurrence risk.

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

In our data set, multiple type initial febrile seizures was the only baseline characteristic and known risk factor that predicted a febrile seizure recurrence at the time the child has fever (Table 5.2.3). In contrast with this finding, other studies concerning risk factors for recurrence show that multiple type initial febrile seizures is a relatively weak factor compared to a positive first degree family history of febrile seizures, a low (below 40.0 °C) temperature at the initial seizure, one or more previous recurrences and time lapse since previous seizure not exceeding six months.[3,4,6,8] The absence of association between the known risk factors and seizure recurrence in the present study should not be interpreted as lack of importance of these risk factors. Only children with an increased risk of febrile seizure recurrences have been included. Selection based on high risk criteria reduces the power of the study to identify these criteria as high risk factors. If also children with a lower recurrence risk had been included, the relative risks might have been different and the known risk factors might have been found associated with seizure recurrence. Further, we have studied recurrent seizures in a different way, i.e. the prediction of recurrences specifically at the time the child has fever, which might explain the different results.

One might argue that we found the temperature the most important predictor of febrile seizure recurrence, because some temperature data were missing; high temperatures might have been measured more frequently than low temperatures. However, it is not very likely that this mechanism has caused a bias in our analysis, because it is unlikely that measuring the temperature is related to the occurrence of a seizure recurrence. However, the main limitation of our study is that the data can not be used to analyze the influence of the rapidity of temperature increase on the risk of seizure recurrence. For the convenience of the participants in the study, the temperature measurements during fever were scheduled at every six hours,

simultaneously to the administering of the study medication, without measurements in between. If continuous data had been available, we might have clarified whether the temperature itself, the rapidity of increase, or both, are the main febrile seizure eliciting factors.

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

Conclusion

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

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6

Genetic aspects

6.1 Characteristics of the initial seizure in familial febrile seizures

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Summary

We studied complex seizure characteristics in patients with a positive family history to define familial phenotype subgroups of febrile seizures. Fifty-one children with one or more affected first degree relatives and 177 without an affected first degree relative were compared regarding history of complex characteristics of the initial febrile seizure. No difference was found in the frequency of febrile status epilepticus (OR=1.1 (0.3-4.3)), multiple type (OR=0.6 (0.3-1.2)) and focal characteristics (OR=0.4 (0.2-1.2)). The presence of any complex characteristic (OR=0.5 (0.3-1.0)) was higher in those without an affected first degree relative, although differences did not reach the level of statistical significance. The familial type of febrile seizures is not associated with complex characteristics of the initial febrile seizure. Complex seizure characteristics are unlikely to help in discriminating phenotype subgroups for genetic studies of febrile seizures.

Introduction

Although the genetic basis of febrile seizures is still unknown, several findings suggest a genetic origin of febrile seizures. Febrile seizures are known to aggregate in families; 18 to 40% of affected children have affected relatives and monozygotic twin concordance varies between 19% and 69%, depending on the sampling method of the study.[1-6] A polygenic aetiology is suggested in some families, in addition to an autosomal dominant inheritance pattern observed in others.[6,7] One study found different inheritance patterns, depending upon whether the patients had suffered recurrent febrile seizures.[8] A positive family history of febrile seizures is one of the major risk factors for febrile seizure recurrence; if first degree relatives are affected, the recurrence risk is increased and may rise up to 80%.[2-5,9] Clearly, the frequency of febrile seizure recurrences is an important phenotype feature of children with a familial type of febrile seizures. An increasing number of genes are identified for epileptic disorders but no genes for febrile seizures specifically have been localised up until now. An important step into the localisation of genes involved in febrile seizures will be the dissection of the heterogeneous group of children with febrile seizures into subgroups of patients with a more homogeneous phenotype.

We examined whether familial febrile seizures can be characterised by complex seizure characteristics. Characteristics of the initial febrile seizure were compared between children with one or more affected first degree relatives and children without an affected first degree relative.

Patients and Methods

Patients

Children who consecutively visited the Sophia Children's Hospital Rotterdam or the Juliana Children's Hospital The Hague between 1994 and 1996 with a febrile seizure were considered for inclusion. They were selected from the prospective febrile seizure registration, established at the paediatric department of the Sophia Children's Hospital Rotterdam since 1988. The paediatric department of the Juliana Children's Hospital The Hague joined this registration in 1994. All patients in this registration visited the febrile seizure outpatient clinic within two to four weeks after a febrile seizure. In addition to routine patient follow-up, baseline characteristics of the patients were registered, including the family history. A febrile seizure was defined according to the NIH-consensus for febrile seizures, excluding any seizure caused by an underlying abnormality and excluding any seizure occurring after a previous non-febrile seizure.[10] Children with an unknown family history were excluded from the analysis. Children with a non-Caucasian origin were excluded to obtain a genetically homogeneous study sample.

Children were included in the case group, if they had one or more first degree relatives affected with febrile seizures: parents, brothers and sisters. The referent group consisted of all children who had no first degree relatives affected by febrile seizures.

Data collection

The following data were studied: baseline characteristics, including age at the initial febrile seizure (age at onset), gender, and the presence of complex characteristics of the initial febrile seizure. A seizure was defined as complex, if the seizure lasted 30 minutes or longer (febrile status epilepticus) and/or if the seizure recurred within 24 hours (multiple type) and/or if the seizure had a focal onset or a postictal Todd's paresis of facial muscles or limbs (focal characteristics).[1,11,12] Seizure characteristics were determined based on the history given by the parents or other witnesses of the seizure, or on the documentation in the patient chart. If characteristics of the initial seizure were unknown, these were considered missing values.

For the analysis, the status affectus of the second and further degrees was not taken into account. Siblings and parents with epileptic disorders but without a history of febrile seizures were considered not affected.

Statistical analysis

The relation between the characteristics of the initial febrile seizure (febrile status epilepticus, multiple type and focal characteristics) in the case group and the control group was estimated using logistic regression analysis. Odds Ratios (OR) were used as the measure of association; associations were statistically significant ($p<0.05$) if the 95% confidence interval of the OR did not include the value one. SPSS 6.0 for Windows was used for the analysis.

Results

Of all 478 children who had visited one of the two participating hospital because of a febrile seizure between 1994 and 1996, 240 children were of non-Caucasian origin. In 10 of the remaining eligible children, the family history was unknown. Thus, 228 children entered the study.

Of them, 51 (22%) children had at least one affected first degree relative and were included in the case group: 14 (27%) of the 51 children had one or more affected siblings, 31 (61%) had one affected parent and 6 (12%) had one affected parent and one or more affected siblings. The referent group comprised 177 (78%) of 228 children without a first degree relative affected by febrile seizures.

Table 6.1.1 shows the baseline characteristics and the characteristics of the initial febrile seizure of the cases and the referents. Using logistic regression, no difference was shown in age at onset and gender. Febrile status epilepticus did not differ between the two groups; multiple type and focal characteristics were counted more frequently in the referent group; the presence of any complex characteristic was observed more frequently in the referent group, although differences did not reach the level of statistical significance (p=0.07). The number of complex characteristics per seizure neither showed a difference between the case and the referent group.

Table 6.1.1 Baseline characteristics and characteristics of the initial febrile seizure

	Cases n=51	Referents n=177	OR (95%CI) Univariable	p-value
Baseline characteristics				
Age at onset[a]	1.3 (1.0-2.2)	1.5 (1.2-2.2)	0.8 (0.5-1.1)	0.19
Female gender	19 (37%)	73 (41%)	0.8 (0.4-1.6)	0.61
Initial seizure characteristics				
Febrile status epilepticus[b]	3 (6%)	9 (5%)	1.1 (0.3-4.3)	0.89
Multiple type[c]	11 (22%)	56 (32%)	0.6 (0.3-1.2)	0.14
Focal characteristics[d]	5 (10%)	27 (15%)	0.4 (0.2-1.2)	0.11
Any complex characteristic	14 (27%)	72 (41%)	0.5 (0.3-1.0)	0.07
Number of complex characteristics[e]				
0	36 (71%)	97 (55%)	rc.	-
1	9 (18%)	52 (29%)	1.5 (0.9-2.4)	0.11
2	5 (10%)	20 (11%)	0.7 (0.4-1.2)	0.21
3	-	-	-	-

[a] median and 25th-75th percentiles (years)
[b] missing values: 3 (6%) versus 19 (11%)
[c] missing values: 3 (6%) versus 14 (8%)
[d] missing values: 12 (23%) versus 72 (41%)
[e] analysed as a continuous variable: OR=0.7 (0.4-1.1), p=0.14
rc reference category

Discussion

This study demonstrates that the familial type of febrile seizures is not likely associated with complex characteristics of the initial seizure. Thus, defining a phenotype subgroup associated with complex seizure characteristics may be unhelpful in genetic studies to localise genes involved in febrile seizures. The study results suggested even higher frequencies of complex seizure characteristics in the referent group, although differences were not statistically significant. These results are supported by a study that showed no difference in 'seizure severity' in familiar versus non-familiar febrile seizures. In the previous study, no further specification was made on how seizure severity was defined and whether or not complex seizure characteristics were considered.[13] Another familial febrile seizures study suggested that the proportion of complex febrile seizures was higher among multi-case (familial) compared to single-case (non-familial) probands. Statistical significance, however, was not reached.[6] The results of the present study are in accordance with these previous studies.

A large population-based study of 2609 relatives (parents, siblings, children, nieces, nephews and half-sibs) of 421 children with febrile seizures investigated the risk for the development of febrile seizures in siblings. Besides frequent recurrent seizures, complex seizures in the proband showed to be associated with an increased risk of febrile seizures in siblings, which may suggest that complex seizures are associated with a familial predisposition.[1] In a recent study of 398 first degree relatives of 129 children with febrile seizures, the risk of febrile seizures in siblings was studied. This risk was increased when the proband had had recurrent febrile seizures. Unfortunately, complex characteristics were not considered in the analysis.[14] These two previous studies have used a different strategy to investigate phenotype subgroups which may be helpful to study the hereditary basis of febrile seizures. Their approach has been based on studying a sample of the *relatives* of the proband. Thus, their results can not easily be compared with ours. Both previous studies provided evidence for recurrent febrile seizures and one of them also for complex seizure characteristics[1], to be interesting phenotype subgroups in studying the hereditary basis of febrile seizures.[1,14]

The limitation of the present study is the high number of missing values regarding focal seizure characteristics. This is likely to be due to the relative difficulty of recognising a focal seizure feature. In a study assessing the accuracy of the classification of complex characteristics of febrile seizures, experienced paediatric neurologists showed most often disagreement regarding assessment of focal seizure characteristics. Their disagreement concerning multiple and prolonged characteristics was clearly lower.[11]

In conclusion, we provided no evidence for association between the familial type of febrile seizures and complex characteristics of the initial febrile seizure of the proband. This does not exclude the existence of other clinical features, i.e. characteristics of the seizure, specific for patients with familial forms of febrile seizures. Complex febrile seizure characteristics, however, are unlikely to help in discriminating phenotype subgroups for genetic studies of febrile seizures.

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6.2 No evidence for febrile seizures linked to genetic markers on chromosome 8q and 20q

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Summary

Introduction Familial clustering indicates a genetic contribution to the predisposition of febrile seizures. One previous study on a large family with multiple affected persons has provided a suggestion for a gene on chromosome 8q for febrile seizures. For benign familial neonatal convulsions (BFNC) evidence for linkage on chromosome 8q and 20q has been described. Because of the clinical association of BFNC with febrile seizures both loci are candidate regions for febrile seizures in the general population.
Patients We have studied markers of chromosome 8q and 20q surrounding the two loci in 72 affected sib pairs with febrile seizures. Of these pairs 55 were of Caucasian origin and 17 were of other origins including Turkey, Morocco, the Philippines and Surinam.
Methods Affected sib-pair analysis was performed on genotypes from five microsatellite markers (D8S1132, D8S592, D8S1179, D20S1085 and D20S171).
Results We found no evidence for linkage between febrile seizures and the chromosomes studied. In the Caucasian sib-pairs linkage to chromosome 20q (52 sib-pairs tested) and 8q (30 sib-pairs tested) could be excluded (lod score -2). The maximum percentage of alleles shared between affected siblings was 68% in the non-Caucasian population on chromosome 20 (multipoint maximum lod score 0.63). This observation, however, is based on 12 sib-pairs.
Conclusions The present study provides no evidence for involvement of loci on chromosome 20q and 8q in febrile seizures. A wide search of the genome and enlargement of the sample is necessary to localise genes predisposing for febrile seizures.

Introduction

Febrile seizures is a common seizure disorder with a prevalence of 3.9% in Dutch schoolchildren.[1] In the United States and Great Britain approximately 2 to 5% of all children has been affected.[2,3] These seizures occur in association with fever during childhood, without an underlying defined cause.[4] There is some evidence for a genetic origin, but the specific contribution of genetic factors as well as the mode of inheritance are still unclear.[5-7]

Suggestions for a genetic locus on chromosome 8q13-21 linked to febrile seizures have been found recently in one large family with multiple affected persons.[8] Febrile seizures are prominent in some families with benign familial neonatal convulsions (BFNC).[9,10] A locus for BFNC has been identified on chromosome 20q, later another locus for BFNC has been

reported on chromosome 8q.[9,11-13] Other linkage studies failed to confirm that these BFNC-genes on chromosome 8 or 20 are implicated in febrile seizures.[10,14] Recently, mutations in a novel potassium channel gene on chromosome 20q13.3 (KCNQ2) were found to co-segregate in large BFNC families.[15] In one BFNC family a mutation in a novel potassium gene in co-segregation with the BFNC phenotype was identified on chromosome 8q24 (KCNQ3).[16] Chromosome 8q locus and perhaps also the BFNC locus on chromosome 20q are candidate regions for febrile seizures in the general population. We have studied several polymorphic markers flanking the loci on chromosome 8q and 20q in 72 sib pairs with febrile seizures.

Patients and Methods

Patients

Families (n=68) were selected using the available clinical data of the patients who had visited the Sophia Children's Hospital Rotterdam between 1988 and 1997 or the Juliana Children's Hospital Den Haag between 1992 and 1997 for a febrile seizure. Two families were included in collaboration with regional hospitals (n=1) and general practitioners (n=1). After an announcement in a popular monthly magazine (1997) 10 additional families were recruited. Written informed consent was obtained from all 80 participating families according to the international guidelines and national legislation. The study protocol was approved by the local ethical review boards.

Families were eligible if there were two or more siblings or half-siblings with febrile seizures in the family. A febrile seizure was defined according to the NIH Consensus Meeting as 'an event (sudden loss of consciousness, eventually accompanied with tonic-clonic muscular contractions) 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'.[4] All participants were interviewed by one of us (MvS). By means of a standard questionnaire the diagnosis was verified according to these criteria. Additional or diagnostic information was asked from the patients' general practitioner, neurologist or paediatrician. Eight families were excluded from the present analysis because the diagnosis could not be verified. Thus, the present study included 72 families.

Familes were defined non-Caucasian if one of the two parents or both parents were of non-Caucasian origin. Otherwise, families were defined of Caucasian origin.

DNA studies

Genomic DNA was isolated from peripheral blood as described by Miller et al.[17] Microsatellite markers were tested in multiplex reactions essentially as described by Weber and May[18] using Amplitaq Gold™ according to the manufacturers protocol. PCR reactions were performed in 96 well plates in a Perkin-Elmer-Cetus 9600 Thermocycler. Initial denaturation was 15' at 95°C followed by 32 cycles of 30" denaturation at 95°C, 30" annealing at 57°C and 90" extension at 72°C. After 25 cycles a final extension time of 5' at 72°C was used. Primers were labelled with three different fluorescent dyes; 6-carbofluorescein (FAM), 4,7,2',4',5',7'-hexachloro-6-carbofluorescein (HEX), and 4,7,2',7'-tetrachloro-6-carboxyfluorecein (TET) and visualised on the ABI PRISM™ 377 as blue, green, and yellow respectively.

Information for microsatellite markers D8S1132, D8S592, D8S1179 (chromosome 8), D20S1085 and D20S171 (chromosome 20) was obtained from the Genome DataBase (GDB).[19] Marker order was also obtained from GDB.

Statistical analysis

Relative population frequencies of marker alleles were estimated from all observed genotypes, with correction for family relationships[20], using the ILINK option of the LINKAGE program package, version 5.03.[21] The following marker order and intermarker distances were used in the multipoint sib-pair analysis: D8S1132 - 6 centiMorgan (cM)- D8S592 - 11 cM - D8S1179 and D20S1085 - 13 cM - D20S171. In addition to the multipoint analysis a single-point analysis was performed.

Affected sib-pair analysis was performed using the MAPMAKER/SIBS programme[22], simultaneously including marker information for all markers in a given chromosomal area, using the 'dominance variance' (non-restrictive) model. To assess whether any discrepancy existed, in addition a 'no dominance variance' (additive) model was used. Using this 'no dominance variance' model we considered a strict function of the number of alleles shared to estimate the risk of disease in siblings. The 'dominance variance' model does not include this restriction; only a higher lod score significance threshold (3.3) has to be defined. When more than two affected sibs occurred in a single sibship weighted scores were computed according to Suarez and Hodge.[23]

In a sib-pair analysis the sharing of parental marker alleles between sibs is evaluated. Normally 25% of sib-pairs share their marker alleles from both parents, 50% share one marker allele from one of their parents, while the remaining 25% share no parental allele. Deviations from this pattern towards increased sharing and consistent with the constraints of Holmans' possible triangle are explained as linkage and expressed as maximum lod score (MLS).[24]

In addition, exclusion analyses were performed for which we used the 'no dominance variance' model. The λ-sib was defined as 2.7, which means that siblings of patients with febrile seizures have a 2.7 times increased risk of developing febrile seizures.[25]

Not all of the 72 families were analysed for both chromosome 8q and 20q. We started with genotyping and analysing a sample of 45 families including both Caucasian and non-Caucasian families for chromosome 8q and 20q. In the next phase of the study 27 families of Caucasian origin were genotyped and analysed for chromosome 20q; of them, 19 were also genotyped and analysed for chromosome 8q.

Results

Study population characteristics

Of the 72 participating families 55 (76%) were of Caucasian origin. In 4 families only 1 parent was available for genotyping. In 14 families there were more than two affected siblings: 13 had three and 1 had five affected siblings. The characteristics of the study population are shown in Table 6.2.1. The median time interval between the initial seizure and study entry was 5.0 (2.3-10.0) years.

Table 6.2.1 Characteristics of the study population (affected siblings)

Characteristics	Total n=160 (100%)
Female gender	77 (48%)
Age at study entry in years[a]	6.2 (3.8-9.2)
History of recurrent febrile seizures	91 (57%)
Initial seizure characteristics:	
Age in years[a]	1.4 (1.1-2.1)
Multiple type[b]	40 (25%)
Febrile status epilepticus[c]	24 (15%)
Focal features[d]	7 (4%)

[a] median (25-75 percentiles)
[b] one or more recurrent seizures within 24 hours
[c] seizure duration of ≥30 minutes
[d] focal onset of the seizure and/or postictal Todd's paresis of facial muscles or limbs

Identity by descent

The results of the total sample are shown in Table 6.2.2. The percentages of alleles shared were generally not higher than 50%, suggesting that a febrile seizure locus is unlikely localised in the regions studied.

Table 6.2.3 and 6.2.4 show the results of separate analyses for the Caucasian and the non-Caucasian families. In the Caucasian families the percentage alleles shared remained close to 50%, with the exception of the multipoint results of chromosome 8q (alleles shared 58%, lod score 0.29, 30 pairs), which was also shown by the overall analysis. Single-point analysis of the D8S1132 marker gave similar results compared to the multipoint analysis. In the Caucasian sib-pairs linkage to chromosome 20q (52 sib-pairs tested) and 8q (30 sib-pairs tested) could be excluded (lod scores lower than -2). The non-Caucasian families showed increased allele sharing on chromosome 20q to 68%, which implies a slight suggestion of linkage (lod score 0.63). Single point analysis for marker D20S1085 resulted in an increased number of alleles shared (75%) with a lod score of 0.87.

Table 6.2.2 Allele sharing in sib-pairs (overall)[a]

Markers	No dominance variance		Dominance variance		% informativeness
	allele sharing	lodscore	allele sharing	lodscore	
Chromosome 8					
D8S1132	0.55	0.18	0.55	0.18	0.74
D8S592	0.50	0	0.50	0	0.42
D8S1179	0.55	0.11	0.55	0.11	0.65
Haplotype/multipoint	0.57	0.34	0.57	0.34	0.64-0.83
Chromosome 20					
D20S1085	0.54	0.12	0.55	0.14	0.50
D20S171	0.50	0	0.50	0	0.55
Haplotype/multipoint	0.51	0	0.51	0.01	0.49-0.64

[a] Number of families tested: n=45 (chromosome 8) and n=64 (chromosome 20)

Table 6.2.3 Allele sharing in sib-pairs (Caucasian subpopulation)[a]

Markers	No dominance variance		Dominance variance		% informativeness
	alleles shared	lodscore	alleles shared	lodscore	
Chromosome 8					
D8S1132	0.58	0.3	0.58	0.3	0.72
D8S592	0.50	0	0.50	0	0.41
D8S1179	0.55	0.09	0.55	0.09	0.71
Haplotype/multipoint	0.58	0.29	0.58	0.29	0.67-0.80
Chromosome 20					
D20S1085	0.50	0	0.50	0	0.45
D20S171	0.50	0	0.50	0	0.66
Haplotype/multipoint	0.50	0	0.50	0	0.49-0.72

[a] Number of families tested: n=30 (chromosome 8) and n=52 (chromosome 20)

Table 6.2.4 Allele sharing in sib-pairs (non-Caucasian subpopulation)[a]

Markers	No dominance variance		Dominance variance		% informativeness
	alleles shared	lodscore	alleles shared	lodscore	
Chromosome 8					
D8S1132	0.50	0	0.50	0	0.78
D8S592	0.58	0.09	0.58	0.09	0.46
D8S1179	0.54	0.11	0.59	0.17	0.53
Haplotype/multipoint	0.55	0.07	0.59	0.29	0.60-0.88
Chromosome 20					
D20S1085	0.75	0.87	0.75	0.87	0.71
D20S171	0.50	0	0.50	0	0.07
Haplotype/multipoint	0.69	0.59	0.68	0.63	0.29-0.74

[a] Number of families tested: n=15 (chromosome 8) and n=12 (chromosome 20)

Discussion

In a previous study a suggestion for linkage of febrile seizures to a locus on chromosome 8q13-21 in one large family with multiple affected persons has been found.[8] BFNC is a seizure disorder occurring in newborns. These seizures have been observed to be followed by febrile seizures in some families.[9,10] A locus for BFNC has been identified on chromosome 20q and later also on chromosome 8q.[9,11-13] The role of these chromosomes in BFNC was confirmed by the finding of co-segregating mutations on chromosome 20q13.3 and chromosome 8q24.[15,16] The localisation of these mutations reveals the implication of potassium channel genes (KCNQ2 and 3) in BFNC. Possibly, these mutations may also be involved in other inherited
types of epilepsy and in febrile seizures. Other linkage studies, however, have failed to confirm that BFNC-genes on chromosome 8 or 20 are implicated in febrile seizures.[10,14] Accordingly, one other recently published study of one large family with multiple subject affected by febrile seizures excluded linkage to the chromosome 8 locus in an extended family with febrile seizures.[26]

The present study failed to show linkage between febrile seizures and the loci studied. Findings were consistent in the families of Caucasian and non-Caucasian origin. The separate analysis of the Caucasian families showed no evidence for linkage of chromosome 8q and 20q. The results of the genotyping of chromosome 20q in the Caucasian families have been not suggestive for a gene on this region of the chromosome. Although a slightly higher percentage of alleles shared (58%) of chromosome 8 was seen in multipoint and single point analysis, the exclusion analysis in the Caucasian sib-pairs showed clearly that linkage to chromosome 20q and 8 could be excluded. The chance to localise a gene has been highest in this sample since this is genetically the most homogeneous group of families. The sample size of the Caucasian families is substantially larger compared to the non-Caucasian sample, which makes the results of the Caucasian families more reliable. The non-Caucasian families showed increased allele sharing on chromosome 20q implying a slight non-significant suggestion of linkage in the multipoint analysis. The single point analysis of marker D20S1085 resulted in an even higher percentage (75%) allele-sharing with a lod score of 0.87. The small non-Caucasian sample consisted of families from a variable origin: Turkey, Morocco, The Philippines and Surinam. These families contributed approximately equally to the results, which makes the presence of linkage less likely. Most important is that the suggestive observation was based on a limited number of informative families and remains to be confirmed.

The suggestion provided by a previous study for a febrile seizures gene localised on chromosome 8q has been based on an analysis of one large family with 19 subjects with febrile seizures.[8] Three of them developed afebrile seizures. Of these three, one subject had temporal lobe epilepsy with hippocampal sclerosis. Although families with such phenotype features were not present in our study this may not explain the contradictive finding, because only one subject had this different type of predisposition. Further, since the patients in our study are children we do not know their precise type of predisposition yet. Our inability to find a significant role of BFNC-genes on chromosome 20q and 8q in the risk of developing pure febrile seizures, however, may be explained by the fact that BFNC did not occur in our population.

Previous work on familial aggregation in febrile seizures suggest that siblings of patients with febrile seizures have a 2.7 to 3.7 times increased risk of developing febrile seizures.[25,27] This suggests that genetic factors play an important role. There is little evidence in our study that the loci on chromosome 8q and 20q involved earlier in febrile seizures and BFNC play an important role in the occurrence of febrile seizures in the general population. Further searching of the genome will be necessary to identify predisposing genes for febrile seizures. To increase the power of the present study to detect linkage, the sample size of the study population needs to be enlarged. Recently provided evidence for a gene for familial febrile seizures on chromosome 19p requires confirmation in other families with febrile seizures including ours.[26]

The present study provides no evidence for involvement of loci on chromosome 20q and 8q in febrile seizures. A wide search of the genome and enlargement of the sample is necessary to localise genes predisposing for febrile seizures.

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7

Informed consent in pediatric studies

7 Informed consent: parental awareness and reasons for participating in a randomised controlled study

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Summary

Background The informed consent procedure plays a central role in randomised controlled trials but has only been explored in a few studies on children.
Aim To assess the quality of the informed consent process in a paediatric setting.
Methods A questionnaire was sent to parents who volunteered their child (n=230) for a randomised, double blind, placebo controlled trial of ibuprofen syrup to prevent recurrent febrile seizures.
Results 181 (79%) parents responded. On average, 73% of parents were aware of the major study characteristics. A few had difficulty understanding the information provided. Major factors in parents granting approval were the contribution to clinical science (51%) and benefit to the child (32%). Sociodemographic status did not influence initial participation but West European origin of the father was associated with willingness to participate in future trials. 89% of participants felt positive about the informed consent procedure; however, 25% stated that they felt obliged to participate. Although their reasons for granting approval and their evaluation of the informed consent procedure did not differ, relatively more were hesitant about participating in future. Parents appreciated the investigator being on call 24 hours a day (38%) and the extra medical care and information provided (37%) as advantages of participation. Disadvantages were mainly the time consuming aspects and the work involved (23%).
Conclusions Parents' understanding of trial characteristics might be improved by designing less difficult informed consent forms and by the investigator giving extra attention and information to non-West European parents. Adequate measures should be taken to avoid parents feeling obliged to participate, rather than giving true informed consent.

Introduction

Informed consent issues relating to clinical research involving children are increasingly attracting professional interest.[1-3] The informed consent procedure plays a central role in randomised controlled trials. However, studies of the issues in clinical trials involving children are limited. Understanding parental comprehension and their reasons for approval may lead to changes in the procedure that could enhance its quality. Based on the information provided, parents decide whether or not to permit their child to participate; therefore we should aim to provide adequate information about the study. Understanding how parents perceive the different aspects of research procedures could lead to improved quality of comfort for children and parents participating in future studies. In addition, compliance might increase and withdrawal might be reduced, factors that would benefit the study itself.

We assessed how parents who had given informed consent for their children to participate in a randomised controlled trial of ibuprofen to prevent recurrent febrile seizures evaluated the information presented. We determined their sociodemographic status, their awareness of major study characteristics, their reasons for granting approval, their perception of the informed consent procedure, the perceived advantages and disadvantages of participation and their willingness to participate in future studies.

Patients and Methods

Patients

The study population consisted of parents or guardians who had volunteered their child for a randomised double blind placebo controlled trial of ibuprofen to prevent febrile seizure recurrences.[4] All children were between 1 and 4 years old, with a recognised risk of febrile seizure recurrence, and parents were Dutch or English speaking. Each child had visited the emergency room of the Sophia Children's Hospital in Rotterdam or the Juliana Children's Hospital in Den Haag because of a febrile seizure. Children (n=230) were included in the trial between 1 October 1994 and 1 April 1996 and followed up until 1 October 1996. The trial procedures complied with Dutch national legislation and international guidelines.[5] The trial protocol was approved by the institutional review boards of the hospitals involved.

Informed consent procedure

Two weeks after their febrile seizure, each child visited the special febrile seizure outpatients' clinic. If children were eligible, the trial was explained verbally after which the informed consent form was presented. Matters discussed included the rationale, design and procedures, medication, risks, possible negative side effects and parents' freedom to withdraw the child at any time. If the parents requested, they received a copy of the signed informed consent form to take home. If they needed time to consider the invitation to participate, a new appointment was made. They were asked to telephone the investigator at fever onset (24 hours a day), to start promptly and to continue administering the study medication every six hours until the child had been afebrile for 24 hours, and to notify the investigator in the event of seizure recurrence. If no fever had been reported, the investigator contacted parents every three months. At every contact parents were reminded of the study details.

Methods

We compiled a questionnaire consisting of structured and semi-structured questions about the sociodemographic status of the parents, how they evaluated the information presented about the study, their awareness of major study characteristics, their reason for granting approval, their perception of the informed consent procedure, the advantages and disadvantages of participation, and their willingness to participate in future studies.[6,7]

In May 1996, we decided to send the questionnaire to the parents of the children whose participation in the trial ended before April 1996. In May 1997, the remaining parents were sent questionnaires. All parents were unaware of the results of the trial and the treatment to which their child had been randomly allocated. Two investigators who had not yet been involved in the trial sent a letter of introduction to parents to introduce the questionnaire and

request their consent. The questionnaire and written instructions were sent two weeks later. The parents of 15 (7%) children were not contacted because: (1) they were lost to follow up during the trial (n=5), (2) they were lost to follow up after completion of the trial (n=8), or (3) they had participated in another febrile seizure research project (n=2). Of the remaining 215 (93%) eligible parents, 32 did not respond to our announcement and request, without giving a reason. Two questionnaires were returned incomplete. Thus, the study population consisted of the parents of 181 (79%) children.

Statistical analysis

Completed questionnaires were coded and analysed.[8] The answers were categorised in groups. Sociodemographic details were defined in categories.[9,10] The association between socio-demographic data and the answers was studied using logistic regression. The significance level was set at 0.05. Multivariable analysis was done with backward regression (p=0.10). Odds Ratios (OR) are given with their 95% confidence interval (CI95%).

Results

Baseline characteristics

The study population consisted of 181 mothers and 155 fathers. There were 26 (14%) single parent families. Table 7.1 summarises the sociodemographic baseline characteristics.

Table 7.1 Sociodemographic baseline characteristics

	mothers (n=181)	fathers (n=155)
Median age in years (25th-75th percentiles)	32.6 (29.0-37.0)	35.6 (31.6-39.5)
West European origin	135 (75%)	118 (77%)
Occupation		
Unknown	2 (1%)	4 (3%)
Low		
Elementary profession	5 (3%)	3 (2%)
Lower profession	21 (12%)	36 (23%)
No profession/housewife	71 (39%)	2 (1%)
High		
Intermediate profession	59 (33%)	73 (47%)
Higher profession	20 (11%)	33 (21%)
Scientific profession	3 (2%)	4 (3%)
Education		
Unknown	2 (1%)	3 (2%)
Low		
Elementary school	23 (13%)	13 (8%)
Lower general secondary education	21 (12%)	13 (8%)
Vocational training (lower level)	31 (17%)	34 (22%)
High		
Higher general secundary education/ pre-university education	23 (13%)	17 (11%)
Vocational training (intermediate level)	46 (25%)	31 (20%)
Vocational training (higher level)	29 (16%)	34 (22%)
University education	6 (3%)	10 (6%)

Comprehensibility of information

Parents of 176 cases (97%) evaluated the verbal information as easy to understand and four (2%) thought that it was difficult to understand. The general information leaflet about fever and febrile seizures and the informed consent form were evaluated as easy to understand by parents of 171 (95%) cases and as difficult to understand by seven (4%), including four parents who evaluated the verbal information as difficult. All seven mothers were of a non-West European origin and the parents of six children were of unskilled occupation and limited education level.

Table 7.2 Awareness of six major trial characteristics

	number (%) of parents (n=181)
Aim of the study	
Assessment of efficacy of antipyretic treatment or ibuprofen to prevent febrile seizures	95 (53%)
Increase understanding of febrile seizures	63 (35%)
Test or invent a new drug in children	17 (9%)
Study of ibuprofen to provoke febrile seizures	3 (2%)
Do not remember	3 (2%)
Reason for signing the informed consent form	
Indication of being completely informed and approval of participation	136 (75%)
Protectional rights:	
for the investigator	14 (8%)
for themselves and their child	12 (7%)
for both	1 (1%)
Do not remember why they had signed it	16 (9%)
Do not remember that they had signed it	2 (1%)
Possible negative side effects	73 (40%)
50% chance of being assigned a placebo	160 (88%)
Random allocation procedure	91 (50%)
Possibility of withdrawing	165 (91%)

Awareness of six major trial characteristics

We asked parents to describe in their own words the aim of the trial. We used a multiple choice question to determine why they thought they had to sign the informed consent form. We assessed the knowledge of the other four trial characteristics (Table 7.2).

Of the three parents who did not remember the aim of the trial, two were not aware why they had signed the informed consent form. Nonetheless, the two parents who did not know that they had signed it understood the aim of the trial.

As expected, all parents who knew about the random allocation procedure (n=91) were also aware of the 50% chance for the child to be assigned a placebo. Eighty two (45%) of the parents were aware of five to six major trial characteristics. This high level of awareness was

associated with two-parent family (OR=3.2(CI95% 1.2-8.4), p=0.02), high education level of the mother (OR=2.3(CI95% 1.3-5.0), p=0.01) and West European origin of the mother (OR=8.6(CI95% 3.4-21.7), p<0.01) and father (OR=6.3(CI95% 2.4-16.7), p<0.01). In the multivariate model, West European origin of the parents was retained.

None of the parents who evaluated either the verbal or the written information as difficult (n=7) could remember more than three of the six major trial characteristics. They had most difficulty with remembering the aim of the trial, the reason for signing the informed consent form, and the random allocation procedure.

Major reasons for granting approval

The major reasons for parents for granting approval are shown in Table 7.3. The largest group consisted of parents whose major reason for participation was to contribute to clinical science (51%). We asked parents if they had felt obliged to participate in the trial; 45 (25%) parents answered affirmatively. We compared the reasons for approval of those parents who had felt obliged to participate with the reasons of those who had not; no significant difference was found.

Table 7.3 Major reasons for approval versus feeling obliged to participate

	Felt obliged to participate	
	No (n=136)	Yes (n=45)
Contribution to clinical science n=92 (51%)	67 (49%)	25 (56%)
Benefit for their own child n=58 (32%)	46 (34%)	12 (27%)
Benefit for other children in future n=5 (3%)	4 (3%)	1 (2%)
Benefit for the parent n=6 (3%)	5 (4%)	1 (2%)
Give something in return for the care of their child n=12 (7%)	9 (7%)	3 (7%)
The doctor asked n=6 (3%)	4 (3%)	2 (4%)
No major reason n=2 (1%)	1 (1%)	1 (2%)

Table 7.4 Perception of the informed consent procedure

	Felt obliged to participate	
	no (n=136)	yes (n=45)
Evaluation of invitation to participate		
Negative n=4 (2%)	2 (1%)	2 (4%)
Positive n=165 (91%)	123 (90%)	42 (93%)
Positive, but objections n=5 (3%)	4 (3%)	1 (2%)
No evaluation n=7 (4%)	7 (5%)	0 (0%)
Sufficient time to decide		
Yes n=174 (96%)	132 (97%)	42 (93%)
No n=7 (4%)	4 (3%)	3 (7%)
Sufficient explanation		
Yes n=174 (96%)	131 (96%)	43 (96%)
No n=7 (4%)	5 (4%)	2 (4%)

Perception of the informed consent procedure
Table 7.4 shows how parents perceived the informed consent procedure when they attended the febrile seizure outpatients clinic. We asked them how they had felt about our invitation to volunteer their child for a clinical research project. Most felt positive (n=165, 91%) and thought it was efficiently planned or they felt the time was convenient for them to consider the invitation. Five parents felt positive but had objections: they had been taken by surprise (n=2) or they felt the invitation was an extra problem to think about (n=3). Four (2%) parents felt negative, because they felt that they had been taken by surprise: two of them felt obliged to participate. Their major reason for approval was to contribute to clinical science. Forty two of the 45 parents who felt obliged to participate (93%) felt positive about the invitation.

Of the seven parents who thought that they did not have sufficient time to decide whether to participate or not, four felt positive and three negative about the invitation, because they felt taken by surprise. There were also seven parents who considered they had not received sufficient explanation; six of them had received sufficient time. Of the 13 parents who had either not received sufficient time or explanation, four felt obliged to participate. Their reasons for approval were: contribution to clinical science (n=3) and benefit of their own child (n=1).

Perception of participation
The major advantages and disadvantages of participation are shown in Table 7.5. The parents answered this question in their own words. One hundred and fifty six (86%) mentioned an advantage and 65 (36%) mentioned a disadvantage of participation.

All parents were asked whether they were concerned or not about possible negative side effects of antipyretic drugs for their child in general: 75 (41%) parents were concerned while 105 (58%) were not.

Willingness to participate in future studies
The results of the questions about the willingness and reasons for future participation in another study resembling our clinical trial are shown in Table 7.6. More than half of the parents (n=109, 60%) were willing to participate in a similar future study. We found willingness to participate again associated with West European origin of the father (OR=2.0(CI95% 0.9-4.2), p=0.08), although the results were not significant. The level of awareness of major trial characteristics did not play a role.

We compared the reasons for being prepared to participate in the future to the initial reasons for approval. Of the 44 parents who were willing to contribute to clinical science, 32 (73%) had initially given this as the main reason for approval. The reason for participating in future studies being the benefit of their own child or other children (n=32) was mentioned initially by 14 (44%) of these parents .

We defined four groups of parents (Table 7.7): (1) those who mentioned an advantage only (n=96), and had the highest percentage willing to participate again (68%); (2) those who mentioned both advantages and disadvantages (n=60), and had a slightly lower percentage willing to participate (58%); (3) those parents who did not mention either an advantage or a

Table 7.5 Advantages and disadvantages of participation

	number (%) of parents (n=181)
Advantages	
Investigator on call 24 hours a day	68 (38%)
Extra medical care and information	66 (37%)
The possible efficacy of the study medication	22 (12%)
No advantages	25 (14%)
Disadvantages	
Temperature measurements and administering of study medication during a fever episode	21 (12%)
Hospital visits at fever onset	10 (6%)
Time consuming aspect and work involved in general	10 (6%)
The possible inefficacy of the study medication	4 (2%)
Other:	
Bad taste of the study medication	3 (2%)
Possible side effects	6 (3%)
Not allowed to administer acetaminophen	4 (2%)
Uncertainty about administering placebo or ibuprofen	6 (3%)
Entering the medical circuit	1 (1%)
No disadvantages	116 (64%)

Table 7.6 Willingness and reasons for participation in a similar future study

	number (%) of parents (n=181)
Willing to participate	**109 (60%)**
Contribution to clinical science	44 (24%)
Benefit for their own child and other children	32 (18%)
Extra medical care and support	19 (10%)
No motive	14 (8%)
Not willing to participate	**14 (8%)**
Time and work involved	7 (4%)
No benefit for their own child	4 (2%)
Uncertainty about receiving placebo or active treatment	1 (1%)
No reason	2 (1%)
Do not know	**58 (32%)**
It depends on the study	4 (2%)
Reluctance to be involved with the hospital	1 (1%)
No reason	53 (29%)

disadvantage (n=20), and had an even lower percentage (35%) willing to participate again; and (4) parents who mentioned a disadvantage only (n=5), and had the highest percentage not willing to participate again, although the number was small (n=2). The third group included the highest percentage not knowing whether or not they would participate.

Table 7.7 Willingness to participate in a similar future study versus advantages and disadvantages of participation

	Willing to participate in a similar future study		
	No (n=14)	Yes (n=109)	Do not know (n=58)
Only advantage (n=96)	3 (3%)	65 (68%)	28 (29%)
Advantages and disadvantage (n=60)	7 (12%)	35 (58%)	18 (30%)
Neither advantage nor disadvantage (n=20)	2 (10%)	7 (35%)	11 (55%)
Only disadvantage (n=5)	2 (40%)	2 (40%)	1 (20%)

Table 7.8 Willingness to participate in a similar future study versus initially feeling obliged to participate

	Willing to participate in a similar future study		
	No (n=14)	Yes (n=109)	Do not know (n=58)
Felt initially obliged to participate			
No n=136 (75%)	11 (79%)	88 (81%)	37 (64%)
Yes n=45 (25%)	3 (21%)	21 (19%)	21 (36%)

Table 7.8 shows an association between willingness to participate in a future study and feeling obliged to participate. Parents who did not know whether they would participate or not included a relatively higher number who had felt obliged initially (n=21, 36%) compared with the parents who were certain about whether or not to participate, 19% and 21%, respectively (OR=2.3(CI95% 1.2-4.7), p=0.02).

Discussion

The levels of education and occupation of the responding parents are similar to the Dutch national data for 1996 on educational and occupation levels.[11] Similar studies have shown varying results: parents who permit their child to participate in clinical research can have the same, a higher, or a lower education or occupation level than those who do not.[1,2,12] There is a relatively open and easy accessible health care system in the Netherlands, which makes selection bias unlikely with respect to socio-economic status.

The informed consent form may have been difficult to read.[13] However, only a few parents evaluated the written information as difficult to understand. In addition, verbal information was evaluated as difficult by a few parents. In general, studies concerning the level of difficulty of informed consent forms conclude that investigators should keep the form simple, use short words and sentences, and avoid medical jargon.[14-17] Although language difficulty was an exclusion criterion for the febrile seizures trial, the linguistic usage was clearly too difficult for non-West European parents. The problem might, at least in part, be resolved by using informed consent forms in native languages.

The degree of awareness of the major trial characteristics was generally sufficient; 45% of parents were aware of five or six trial characteristics. A high level of awareness was associated with West European parental origin. Parents who had mentioned difficulties with

understanding the information provided also had difficulties with recalling the trial characteristics. In general, parents understood the details of the trial, despite the difficult informed consent form. Detailed and repeated explanation of the study by the investigator might have played a positive role.[18] In non-West European parents, cultural differences regarding health might also have contributed to difficulties in understanding the information provided.

Half the participants (53%) correctly expressed the aim of the trial. In adult trials these percentages vary between 60% and 87% [18-20] compared with 97% in a paediatric study.[21] In our study we asked parents to describe the aim of the study in their own words. This is a more difficult task, which might explain our relatively low percentage. In future, we will ask parents to describe the aim of the trial in their own words at the time that they are invited to participate and informed consent is discussed.

In our study, all parents were aware that they had participated in a clinical trial, although we are doubtful about the two parents who knew neither the aim of the study nor the reason for signing the informed consent form. Studies involving adult participants show a similar awareness of between 86% and 98%.[18,19]

A signed informed consent form is a legal requirement instituted for the protection of participants. In our study, 75% of participants knew why they had to sign the informed consent form, which indicates a minor inadequacy in this respect. Another paediatric study has shown that only 19% knew the reason for signing; a larger group thought it was to protect the doctors.[21]

The information about possible negative side effects was recalled by 40% which, in our opinion, is low. Only a few parents mentioned negative side effects as a disadvantage of participation and most claimed not to be concerned about the side effects of antipyretic treatment in general. A varying percentage (between 4% and 78%) has been shown in studies in which adult participants were involved, with the higher percentages in oncology trials as compared with antihypertensive treatment studies.[18,20,22] The low recall in our study is unlikely to have resulted from the way in which we presented the information, because the informed consent form describes all negative side effects reported, in a similar way to the standard instruction leaflet for ibuprofen syrup. Low recall might be explained by the relative safety of ibuprofen and the fact that assessment of drug safety was not the aim of the trial.

Similarly, parents were also highly aware (88%) of their child's chance of receiving placebo. Only 3% of parents mentioned this as a major disadvantage of participation; for one parent this was the reason for refusing to participate in a future trial. In a paediatric study of paracetamol, over half of the parents refused to participate, mainly because of a reluctance to risk being assigned a placebo.[12] In adult studies the awareness of this risk is much lower (56%) compared to our study, which might, at least in part, be explained by parental fear of a recurrent febrile seizure.[20,23,24]

The random assignment procedure was recalled by half of parents. All parents who knew about the random allocation procedure were also aware of the 50% chance of being assigned a placebo. In adult clinical trial participants, this issue plays a role as well; awareness of the

random assignment procedure varies between 47% and 75%.[18,19,20] The fact that the parents trust the investigator implicitly in knowing what is best for their child might explain this lower awareness level.[2] In addition,' random assignment' is a theoretical concept, which is difficult to explain. A concrete example of drawing lots might be given.

The possibility of withdrawing from participation at any time was remembered by most parents (91%). One paediatric study [21] showed a much lower level (45%) compared to 44% to 87% in adult studies.[18,19,22]

Parents can be encouraged to participate in clinical research. This is best illustrated by the relatively high participation rate (84%) among the patients who were eligible for our febrile seizures trial [4] compared with other febrile seizure studies (50% to 99%).[25-29] Secondly, the response rate (79%) to our questionnaire study was high compared to other paediatric informed consent questionnaire studies (59% to 70%).[1,2] The high participation rate in our trial might be explained by the setting of the initial invitation to participate: a special outpatients' clinic for febrile seizures in a quiet environment with sufficient time and attention.

In our study, 32% of parents stated they participated for the benefit of their own child. This was a consistent motive, although not as frequently expressed as the willingness to contribute to clinical science (51%), which was the main and most consistent reason of parents to participate. We found that a high percentage of parents in our study (60%) were willing to participate again in the future. This was associated with a West European origin of the father. Other studies have shown that a substantial number of patients are willing to participate, even without being adequately informed about the benefits and risks [2,3,21,22] and despite the fact that it will cost them time and effort.[1,22,30] A more reserved attitude towards participation of their child in clinical research was found in one of these studies: 21% of the parents were prepared to participate for the benefit of other children, contribution to clinical science and confidence in physicians, while 74% would refuse because of the risk of side effects and unproved efficacy of the trial medication.[2] The attitude on the part of parents might have been influenced negatively by the study design; the investigators asked only hypothetical questions instead of questions addressed to parents who were actual participants. Obviously, one's own benefit is a main reason for participation, but the benefit for future patients and the contribution to medical science prevail.[1,2,19,30] We feel this generally positive attitude towards clinical research is positive and promising for future studies. Extra attention should be given to non-West European trial participants to increase their willingness to participate.

We found a substantial number of parents mentioning the time consuming aspect and the work involved as a major disadvantage of participation; a small group of parents (4%) thought that they would refuse to participate in a similar study for this reason. Furthermore, participating parents who did not mention an advantage were more hesitant to agree to participate in a similar future study. If they mentioned an advantage of participation they were prepared to put up with disadvantages; disadvantages play a minor role in future participation.

We were not sure how parents would experience being asked to participate during their appointment at the special febrile seizure outpatients' clinic. We found that 25% of the parents felt obliged to participate. This might be related to the feeling of being dependent on

the investigator or the hospital. A relatively large number of those hesitant to participate in a future study were among the parents who felt obliged to participate. However, of the parents who felt obliged to participate only two (4%) approved because the doctor asked. Other explanations might be that they felt forced to participate because of their responsibility, either owning to the rather frightening disease of their own child, other children, or scientific development in general. We showed that parents who felt obliged to participate have similar major reasons for granting approval and a similar evaluation of the informed consent procedure compared with parents who do not feel obliged, indicating that they do not differ as much as one might assume. However, we consider the fact that parents felt obliged to participate as a failure of our informed consent procedure, because feeling obliged to participate might exclude giving truly informed consent. The involvement of a third party (such as a research nurse), to provide parents with information and to invite them to participate, might be advisable.[18] We offered parents some time for reflection, if they so requested; a compulsory time period for parents to consider the matter might also be implemented to improve the procedure.

One of the limitations of this study is the number of parents (14%) who did not respond to the questionnaire. We do not know their reasons, but it might be that they would evaluate our trial less positively than those who were willing to fill in the questionnaire. Thus, we might have overestimated the generally positive evaluation of the trial. Furthermore, the questionnaire we used has not been completely validated. The questions concerning sociodemographic status, awareness of major study characteristics, and advantages and disadvantages of participation were formulated using the Lynn method [6], which has been used in other studies.[1,20,30] We tried to minimise implied value judgements in our questions, but the difficulty encountered in all questionnaire studies regarding participants' tendency to give socially desirable answers inevitably played a role in our study too. However, we think that the results of our study are relevant to comparable study populations with respect to the subjects (children), the design (randomised, placebo-controlled), the disease (good prognosis but distressing), and the treatment (safe and not invasive).

Conclusion

Parents' understanding of trial characteristics might be improved by a less difficult informed consent form and by the investigator giving extra attention and information to non-West European parents regarding linguistic problems and paying more attention to cultural differences, even in the absence of language difficulties.

The contribution to clinical science and the benefit of the child are major factors in the recruitment of participants. With respect to willingness to participate, advantages of participation are more important than disadvantages. Sociodemographic status does not influence initial participation, but the origin of the father might determine his willingness to participate in future trials. Some parents feel obliged to participate; therefore adequate measures should be taken to ensure that informed consent is genuine.

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8

General discussion and future prospects

8.1 Diagnostic aspects

Biochemical parameters

The evidence regarding the redundancy of routinely performed laboratory tests in children with febrile seizures has been growing. In the United Kingdom and the USA consensus has been reached and established in guidelines for diagnostic procedures in children presenting with a febrile seizure.[1,2] The British guidelines give recommendations on diagnostic tests in children with febrile seizures in general.[1] The American guidelines discuss laboratory investigations in the first simple febrile seizure.[2] Both state that measurement of blood electrolytes, calcium, phosphorus, magnesium and glucose should not be performed routinely. They recommend to perform a glucose test only, if the patient is still convulsive at hospital admission or has a prolonged postictal period of unconsciousness.

Previous febrile seizure studies described association between abnormal biochemical blood test results and complex seizure characteristics, and association between abnormal test results and gastrointestinal disease.[3-14] Table 8.1 summarises the indications for measurement of serum glucose, calcium and sodium, following these previous studies and the international guidelines. The previous studies have shown that the prevalence of abnormal findings in children with febrile seizures is very low. This has resulted in the recommendation not to perform biochemical blood laboratory tests on a routine basis. Although complex characteristics were associated with higher prevalences, laboratory tests have not been recommended as a routine proedure in all children with complex seizures. The guidelines' recommendations when to perform a glucose test have not been based on the prevalence of hypoglycaemia, which is very low, but may be based on potential severe consequences of hypoglycaemia including cerebral damage. If hypoglycaemia is the cause of the seizure this child needs immediate intervention.

The results of our study (chapter 2.1) are represented in the rightmost column of Table 8.1. We have confirmed the low prevalence of hypoglycaemia in children with febrile seizures: none was found. In our study the prevalence of hypocalciaemia (11%) and hyponatriaemia (32%) can not be considered low. Most of the previous studies, however, used lower reference levels to define these abnormalities. We aimed to study the probability of *normal* test results. Most of the abnormalities we found were mild and did not need further evaluation or treatment. The associations in our study given in Table 8.1 have been based on the results of the prediction models of normal findings and the score chart (Table 2.1.3). The most important associations with abnormal test results of calcium and sodium were seizure duration longer than 15 minutes (calcium), vomiting and diarrhoea (calcium) and multiple type seizures (sodium).

Based on the summary in Table 8.1 we suggest that glucose tests should be performed in children who are still convulsive at hospital admission or who have a prolonged postictal period of unconsciousness. The test is mainly used to exclude a severe underlying cause. A sodium and a calcium test may be indicated in children with a seizure duration of more than 15 minutes, in children with a multiple type seizure or in children who have a history of

Table 8.1 Indications for laboratory blood tests of biochemical parameters in febrile seizures previous studies, international guidelines and study results (chapter 2.1)

Parameter	Previous studies	International guidelines[a,b]	Chapter 2.1[c]
Glucose	F: very low prevalence of abnormalities, higher prevalence in complex seizures I: not indicated	still convulsing child prolonged postictal period	F: no abnormalities I: not indicated
Calcium	F: very low prevalence of abnormalities, higher prevalence in complex seizures I: not indicated	not indicated	F: 11% abnormal (1.90-2.18 mmol/l), associations with seizure duration > 15 minutes and vomiting/diarrhoea I: not indicated
Sodium	F: low prevalence of abnormalities, higher prevalence in multiple type seizures I: substantial fluid loss or dehydration	not indicated	F: 32% abnormal (126-134 mmol/l), association with multiple type seizure I: not indicated

[a] British Guidelines, BMJ 1991
[b] American Guidelines, Pediatrics 1996
[c] Based on score chart for calcium and sodium separately (chapter 2.1 Table 5).
F Findings
I Indications

vomiting or diarrhoea. In mild abnormalities re-examination of the child is indicated and eventually retesting until levels are normalised. In the severe cases further diagnostic procedures and treatment will be necessary.

In the decision whether or not to perform a diagnostic test 'common sense clinical practice' plays a major role. The guidelines and the score chart may just give some extra help in the decision process. The prediction model of finding normal biochemical blood test results in children with febrile seizures which we described in chapter 2.1 has been based on various combinations of patient characteristics. The score chart may be used in the individual patient in addition to the recommendations just discussed. A low predicted probability of a normal test result in the individual patient has to be considered an argument to perform the test, and vice versa. Because the discriminative ability of the constructed models is limited, as was the sample size of the study, further validation of the prediction models is necessary in larger populations.

Infectious parameters

In the diagnostic evaluation of children with febrile seizures, increased leukocyte counts in the peripheral blood are often considered a result of the seizure itself, due to stress reactions, especially if prolonged seizures (febrile status epilepticus) are involved. There is some evidence for this assumption based on animal and clinical studies.[15-18] These studies, however, have not addressed children and especially not children with febrile seizures. Young children have an immature nervous system and compared to adults a different physiology. Thus,

extrapolation of evidence from animals and human adults may not always be possible. One study has addressed stress induced reactions on cerebrospinal fluid and blood glucose levels in children with febrile seizures.[19] No difference was found in glucose concentrations in simple versus complex seizures, which may suggest that both seizure types, including long lasting seizures in the complex seizure group, are associated with a similar level of stress.

To assess the association between increased leukocyte counts and seizure duration, children with febrile seizures were studied (chapter 2.2). We reported none of the characteristics of the seizure, including seizure duration, to be associated with an increased leukocyte count. Based on these results, earlier findings may not be applicable to children with febrile seizures. In accordance with the guidelines [1,2] we state that peripheral blood leukocyte counts (and WBC-differentiation parameters) should be used to assess the origin of the fever causing illness, if any clinical suspicion exists of an infection which may dictate further treatment. Routine testing of the leukocyte count in children with febrile seizures is not indicated.

8.2 Parental fear and primary prevention

Studies performed in 1978, 1981 (United Kingdom) and 1991 (Denmark) have described parental anxiety due to the febrile seizures of their child.[61-63] Most parents think their child is dying when it suffers from its initial seizure. After a febrile seizure has occurred they become afraid of fever affecting their child. Parental psychological problems mainly consist of sleeping problems which have been frequently reported. Anxiety is likely to persist even after consultation of their general practitioner or pediatrician. Large follow-up studies show that psychomotor development and intellectual performance are normal in children with febrile seizures.[20-22] The extreme anxiety of parents caused by febrile seizures is thus not in accordance with the excellent prognosis. The results of our questionnaire study among the parents of the participants of the randomised trial presented in chapter 4 have confirmed the earlier findings described in the literature. By means of a mailed questionnaire we have addressed parents' perceptions and knowledge about fever and febrile seizures. We concluded that about half of the parents were afraid or very afraid of fever (Table 3.2). Their fear of fever affecting their child was strongly associated with being afraid of recurrent febrile seizures. Consequences of this parental fear included frequent temperature measurements and remaining awake at night during fever. These activities possibly affect a normal night's rest of the parents (Table 3.3). Further, we described that 47% of the parents thought that their child had been dying when it suffered from the initial seizure (Table 3.4). In a study among parents of children with febrile seizures recently carried out in Israel (n=46), it was found that 60% still reported being very anxious despite the reassuring information provided by the hospital after the seizure had occurred.[23] The other 40% of the responding parents claimed full relief compared to what they had felt at the time of the acute event. Of the parents in our study, 21% said reassuring information had helped them to consider febrile seizures not to be harmful. According to our findings, a family history of febrile seizures, possibly a factor increasing parental experience with febrile seizures, did not influence parental fear. Special diagnostic tests, i.e. electroencephalography and lumbar puncture, increased parental anxiety.[23] Hospital

admission of the child yielded some relief in 34% and no relief in 27%, although one other study suggested that routine hospitalisation may increase parental anxiety.[4] We have not studied the influence of special diagnostic tests and hospitalisation on parental anxiety. Generally, the information provided to the parents by the hospital staff may lack reassurance, may have insufficient clarity or may be provided at a non-optimal moment. Intensive effort is required to relieve parental anxiety after febrile seizures. Parental health education has shown to be effective. Information about fever has been reported to result in improvement of parental confidence and a subsequent decrease in emergency hospital visits for febrile illnesses.[24]

As we discussed in chapter 4, special attention to the provision of information should be paid to parents of a different language and culture. Because they are more frightened compared to parents from Dutch origin they may need information which is tailored to their language and culture. We have confirmed the results of a previous study of parental fear among parents of children with epilepsy which showed that a different language and culture may be associated with an increased fear of seizures.[25]

Information provided immediately after the acute event may be less effective than after for instance two to four weeks. During a follow-up visit the seizure may be discussed again, parents may be told about the excellent prognosis and measures may be taken to prepare them for recurrent seizures.[23] This was the procedure in our study, but unfortunately parents remained anxious.

We propose to provide information to the parents in an earlier stage. Since febrile seizures are a frequent event, occurring in 4 to 5% of children and tend to find the parents unprepared, the question rises if not all parents should be provided information about febrile seizures. If so, then of each 100 parents who will be given information only 4 will actually have to deal with febrile seizures: 96% of the children will never be affected.[26] Negative effects of providing information may entail increasing fear of fever and may increase medical consumption. Balancing the possible positive and negative effects we advocate providing routine information about febrile seizures on a regular basis in the child health centre or well-baby clinic. This suggestion has been made before.[23] The relatively high prevalence of febrile seizures, the extreme parental fear at the moment they witness a febrile seizure in their child and the excellent prognosis of febrile seizures may be the strongest motives for discussing febrile seizures with every parent.[61-63] Minimal information about febrile seizures should entail a description of the typical attack, the benign character and how to act in the event of a seizure, mainly consisting of contacting the general practitioner for an assessment of the risk of meningitis.[27] Antipyretics are not necessary, they should be used moderately and only to make the child feel more comfortable. If antipyretics are used they should preferably be administered at regular intervals, i.e. every six hours (chapter 4), because it is unknown whether one single dose or irregularly administered doses may provoke seizure recurrences.

8.3 Preventive treatment of recurrences

Previous studies

Although febrile seizure recurrences do not affect the risk of non-febrile seizures, psychomotor developmental problems or brain injury prevention in a safe and simple way remains desirable.[28-30] But as all options have either proved to be of debatable efficacy or to be associated with serious negative side effects preventive treatment of febrile seizure recurrences has become questionable.[31] Continuous treatment with phenobarbital has become obsolete.[1,31-33] In a review study, published in 1984, the results of 7 studies of valproate and phenobarbital in febrile seizures regarding preventive efficacy and side effects were compared.[32] Two studies showed a significant reduction in recurrences in children treated with valproate. None showed risk reduction in the phenobarbital group compared to placebo. Side effects were more serious and more frequently reported in the phenobarbital group. A metaanalysis of 7 British trials was published in 1988.[33] Based on the overall preventive efficacy of phenobarbital (OR:0.8 (CI95%:0.5-1.2)), valproate (OR:1.4 (CI95%:0.9-2.4)), and adverse effects it was concluded that neither treatment can be recommended. In a recent metaanalysis published in 1997 the data of 9 randomised controlled trials were studied.[31] Continuous phenobarbital significantly reduced the recurrence risk (OR:0.5 (CI95%:0.3-0.9), four studies); intermittent phenobarbital showed a similar risk reduction but this was not statistically significant (OR:0.5 (CI95%:0.1-2.6), one study); valproate administered continuously was significantly effective (OR:0.1 (CI95%:0.01-0.8), one study). Intermittent treatment with diazepam has beenrecommended, especially after publication of a randomised controlled trial in which 406 children participated.[34] Children with an increased risk, whose parents recognise a febrile illness at an early stage, would benefit from it. The metaanalysis, however, showed that intermittent diazepam was not significantly reducing the recurrence risk (OR:0.8 (CI95%:0.5-1.2), three studies including the large clinical trial mentioned and two smaller studies.[31] It was concluded that intermittent diazepam is a debatable option. Other studies investigated antipyretic preventive treatment.[35,36,84] They concluded that antipyretic treatment is not effective in preventing recurrent febrile seizure. None of these previous studies had a randomised antipyretic-placebo controlled trial design (Table 4.4).

Intermittent antipyretic treatment: study in this thesis

As a contribution to finding an effective preventive intermittent therapy with only minimal side effects we carried out a randomised placebo-controlled trial in 230 children with an increased recurrence risk, using ibuprofen as the preventive alternative (chapter 4). Ibuprofen showed to be a strong antipyretic drug in an adequate 6-hourly dose of 5 mg/kg bodyweight. Both the intention-to-treat analysis and the per-protocol analysis, however, showed ibuprofen to be ineffective in preventing recurrences (HR:0.9 (CI95%:0.6-1.5)).

Generally, data collected in a randomised controlled trial are analysed according to the 'intention-to-treat' principle. This means that, regardless of compliance with the protocol, all eligible patients are compared in their randomly assigned treatment groups. This is the

pragmatic approach providing a more valid assessment of treatment effectiveness as it relates to actual clinical practice.[33,37,38] Alternatively, we may analyse only those subjects, who have been treated with the treatment to which they have been allocated: 'per-protocol' analysis. This is done especially when a substantial number of study participants failed to take the prescribed medication, as was the case in our randomised trial in 178 (32%) of all 555 fever episodes (Table 4.2). This alternative approach is explanatory, as it aims to study the pharmacological efficacy. It is questionable, however, if an unbiased estimate of efficacy will be obtained in this way. Non-compliance may be related to (known and unknown) factors affecting the risk of the outcome under study.[39] Thus in a per-protocol analysis the prognostic balance, which is hopefully the result of randomisation, is likely to be disturbed. Reduction of the sample size and a decrease of the validity of statistical test procedures are relative minor problems of the per-protocol approach. Because of the disadvantages of per-protocol analysis every clinical trial report should contain a primary analysis based on intention-to-treat. Secondary analyses may be performed considering only the data of compliant patients. Thus any difference between the results of these two different methods of analysis is clearly demonstrated and may enlighten interesting explaining mechanisms.[40,41] Following this strategy we found no differences between the intention-to-treat analysis and the per-protocol analysis.

In pediatric practice it is suggested that intermittent antipyretic treatment may provoke seizure recurrences by making the temperature vary between high (before administering a dose) and low (after a dose) temperature. Based on the study results we may conclude that ibuprofen administered six-hourly does not significantly *induce* seizure recurrences. Antipyretics may be safely used to make the feverish child feel more comfortable. It should be clear, however, that prevention of seizure recurrence will be beyond reach.

In view of the risk factors, which have been shown to increase the seizure recurrence risk (the frequency of fever episodes (chapter 5.1) and the temperature at fever onset (chapter 5.2)), it is not easy to understand the inefficacy of antipyretic preventive treatment to prevent febrile seizure recurrences. Perhaps a higher dose of ibuprofen would have shown to be effective, although we confirmed in a previous study that ibuprofen 5 mg per kg has a strong fever reducing efficacy in children with febrile seizures, which has been the basis for using this dosis in the present randomised controlled trial.[42] The risk of negative side effects of a higher dose may increase, although short term studies have not reported a difference in adverse effects associated with 5 mg and 10 mg ibuprofen per dose.[43-45] Antipyretic treatment with ibuprofen is associated with a delay in maximum fever reducing efficacy of about 4 hours.[43-46] This reflects the fact that a complex interaction of numerous factors in addition to drug concentration (which is maximal at 1 hour after onset of treatment) determine the antipyretic response.[46] This includes the sequence of inhibition of prostaglandin synthesis leading to lowering of the hypothalamic set point which puts a series of physiologic responses going. As most recurrent febrile seizures occur early during fever this delay in fever reducing efficacy will remain an additional problem in the prevention of recurrences, which may not be easily solved. Another problem associated with the early occurrence of recurrent febrile seizure is that they frequently are the presenting sign of fever. In our study (chapter 4) we found that in 22 of the 67 recurrences the study medication could not be administered in time, because the seizure was the presenting sign of fever. Early detection of fever is a substantial problem in the prevention of recurrences if intermittent treatment is considered.[34,47-49]

One of the findings to be further investigated is that no difference was found in temperature reducing efficacy in ibuprofen compared to placebo in the fever episodes with a seizure recurrence, based on the defined six-hourly temperature measurements. The 'per-protocol' analysis showed similar results in the course of the temperature compared to the 'intention to treat' analysis (Table 4.3). Thus the high percentage of children who have not used the study medication before the recurrence occurred (55% of the fever episodes with a seizure recurrence) is not likely to be the only explanation of the inefficacy of ibuprofen to reduce fever in those fever episodes. As the temperature reducing efficacy of ibuprofen is at its maximum at four hours after administration the six-hourly measurements may have given an underestimation of the fever reducing effect.[43-46] Since we found a substantial temperature reducing effect in the ibuprofen group when we analysed all 555 fever episodes, underestimation of the fever reducing effect may only be a part of the explanation. Possibly, a higher dose of ibuprofen or another strong fever reducing method could effectively reduce the temperature in those fever episodes in which a recurrence occurs. Another part of the explanation may be the fever causing agent playing a role in the ineffectiveness of antipyretic treatment to lower the temperature in children with a seizure recurrence in the corresponding fever episode. There is evidence, however, that the reduction in body temperature of children receiving antipyretic treatment does not differ between infectious outcomes.[43,50]

To get a better insight into the pathophysiological mechanism of seizure recurrence infectious agents in children with febrile seizure recurrences may be investigated in future studies. Polymerase Chain Reaction (PCR) is a relatively new diagnostic method to assess the cause of fever in a quantitative way.[51-55] Based on previous findings in this context we could start with studying primary infection with human herpesvirus (HHV) 6 and 7 in children with febrile seizures.[56-58] These infections can be diagnosed using PCR techniques on saliva and leukocytes and have been shown to be associated with the occurrence of febrile seizures; in the leukocytes the viral load can be measured quantitatively.[59,60] Then, the efficacy of antipyretics in fever reduction and prevention of recurrence might be assessed in a comparison between children with febrile seizures with and without positive PCR-HHV results.

Pro's and con's of prevention

Prevention of febrile seizure recurrences serves two purposes: meeting parental fear of recurrences in general[61-64] and reducing the risk of a long lasting and eventually injurious seizure.[28-30] Febrile seizures, however, even the long lasting and the frequent recurrences, are associated with a very small, probably not even existing risk of injury.[28-30] Furthermore, there is no evidence that in children with febrile seizures developing epilepsy prophylaxis of recurrent febrile seizures would have prevented it.[65-68] Therefore, prevention of recurrences does not improve the prognosis. Negative consequences of trying to prevent febrile seizure recurrences must also be considered.[69-71] In clinical trials for intermittent treatment of children with febrile seizures, the parents unavoidably focus on any sign or symptom of a febrile illness in order to start treatment immediately at fever onset. They may become obsessed by their child's behaviour, its feverish symptoms and the thermometer.[72,73] The consequence of this focusing on prevention of seizure recurrence may entail an iatrogeneous fear of the parents and indirectly of the child. Editorials have been addressing this subject of pro's and con's of

prevention of febrile seizure recurrences. They conclude that the efforts should focus on reduction of parental anxiety by providing information about the excellent prognosis of febrile seizures.[69-71]

8.4 Prediction of febrile seizure recurrence

Risk factors for seizure recurrence: previous studies

Previous studies have investigated risk factors for seizure recurrence. Although not all studies found similar associations, some factors have been shown to be quite consistent throughout these studies. Table 8.2 shows all the studies published since 1977 which have investigated risk factors for febrile seizure recurrence.[5,74-86] In these studies children with an initial febrile seizure were included. They have studied the association between patient characteristics, characteristics of the initial seizure, the family history and other factors versus the occurrence of a first recurrent seizure or at least one recurrent seizure. Three studies have additionally investigated factors associated with further recurrences.[80,83,86] Table 8.3 illustrates the risk factors which have been associated with the first seizure recurrence, in previous studies and in our studies (chapter 4 and 5). All risk factors which were significantly associated with seizure recurrence had risk estimates in the same direction (>1.0). Table 3 also illustrates which factors have not been associated with seizure recurrence and which factors have not been studied. The study numbers in Table 8.3 correspond with those in Table 8.2.

If the sample sizes of the studies are weighed in Table 8.3 five risk factors show up in decreasing order of importance: young age at the initial seizure, family history of febrile seizures, low temperature at the initial seizure, multiple type initial febrile seizure and short period of fever before the initial seizure. We define these factors as 'known' risk factors and consider them as important factors.

Risk factors for seizure recurrence: studies in this thesis

The study described in chapter 4 of this thesis (study 15 in Table 8.2) has been designed to assess the efficacy of administering ibuprofen during fever to prevent a recurrence. Children with an increased recurrence risk were included, disregarding the number of previous febrile seizures; 36% of all patients had suffered at least one seizure recurrence before study entry (Table 8.4). The outcome was the first recurrence after study entry. Using Cox regression analysis we have re-analysed these data to predict febrile seizure recurrence. We used the complete sample (n=230) because ibuprofen showed not to be effective. The results are given in Table 8.4. In accordance with previous studies we found young age at the initial seizure and multiple type initial febrile seizures to be significantly associated with febrile seizure recurrence. Female gender was also significantly associated with recurrence in our data, which has never been described in previous studies. Caucasian origin, day nursery care, long

duration of the initial seizure and family history of febrile or any other seizures were associated with a *reduced* recurrence risk. Previous studies have shown that a positive family history increases the recurrence risk, which is the opposite of what we described. The associations we found, however, were not significant. Low temperature at the initial seizure (HR=1) was not associated with febrile seizure recurrence. Thus, this characteristic being a strong risk factor as shown in several previous studies could not be confirmed. The results of the present study confirmed previous findings that focal initial seizure and previous recurrent seizures are associated with an increased recurrence risk. In our study, however, these associations did not reach the level of statistical significance. Risk factors of seizure recurrence clearly confirmed by our data were young age at the initial seizure and multiple type initial febrile seizures. These characteristics were significantly associated with an increased risk, as has been described in earlier studies.

In the study of the number of fever episodes in association with febrile seizure recurrence (chapter 5.1, study 16 in Table 8.2) the placebo group of the randomised controlled trial (n=89) and children participating in the cohort study (n=66) were enrolled (a total of 155 children). In the univariable logistic regression model no association between 'known' risk factors and febrile seizure recurrence was found. Age at study entry (OR=0.6 (0.3-1.1) per year increase) and the number of fever episodes (OR=1.8 (1.4-2.4)) were associated with febrile seizure recurrence. In the multivariable model only the number of fever episodes was retained. Three other studies have defined the importance of the number of fever episodes in assessing the risk of seizure recurrence.[78,84,85] One of these studies was a randomised controlled preventive trial which included children with an initial seizure and an average recurrence risk.[85] In addition to the number of fever episodes, two of these studies found positive family history associated with a febrile seizure recurrence.[78,84] We did not find an association between family history and seizure recurrence.

In the study which showed that age and temperature at onset of fever were predictors of seizure recurrence (chapter 5.2., study 17 in Table 8.2) the data of all patients who participated in the randomised controlled trial were considered (n=230).

We constructed a scatter diagram to depict the temperature related to the first febrile seizure recurrence for each child, for which we used all temperature measurements in the 509 fever episodes (Figure 8.1). The figure illustrates that in the time period two hours or more after fever onset the temperature was higher if a seizure recurrence occurred compared to the temperature if seizure recurrence did not occur.

A second diagram was constructed using all temperatures measured in the fever episodes in which a seizure recurrence occurred at two hours or more after fever onset.
Figure 8.2 illustrates the course of the temperature in the individual patients during the fever episodes from fever onset until seizure recurrence. This figure illustrates that the temperature at seizure recurrence was higher compared to the temperature at fever onset. We performed a Poisson regression analysis to study the association of baseline factors, factors unique for each fever episode (age and temperature at onset) and factors unique for each six hours time interval of fever (temperature) with febrile seizure recurrence. Multiple type initial febrile seizures were associated with seizure recurrence. Young age at onset of fever, which might be considered related to young age at initial seizure and short time lapse since previous seizure,

Table 8.2 Studies of risk factors for febrile seizure recurrence

Study number and first author	Journal, Year of publication	Sampling	Sample size
1 Wolf	Pediatrics, 1977	Hospital-based	355 (RCT)
2 Nelson	Pediatrics, 1978	Cohort	1706
3 Knudsen	Arch Dis Child, 1985	Hospital-based	137
4 Verity	BMJ, 1985	Cohort	290
5 Shirts	Neurology, 1987	Cohort	687
6 Knudsen	Acta Neurol Scand, 1988	Hospital-based	137
7 El-Radhi	Arch Dis Child, 1989	Hospital-based	154
8 Berg	J Pediatr, 1990	Meta-analysis[a]	4414
9 Berg	N Engl J Med, 1992	Hospital-based	347
10 Offringa	Dev Med Child Neurol, 1992	Hospital-based	155
11 Offringa	J Pediatr, 1994	Pooled analysis[b]	2496
12 Rantala	Acta Neurol Scand, 1994	Hospital-based	169
13 Uhari	J Pediatr, 1995	Hospital-based	180 (RCT)
14 Berg	Arch Pediatr Adolesc Med, 1997	Hospital-based	428
15 Chapter 4	Pediatrics, 1998	Hospital-based	230 (RCT)
16 Chapter 5.1	Acta Paediatr (submitted), 1998	Hospital-based	155
17 Chapter 5.2	Arch Pediatr Adolesc Med, 1998	Hospital-based	230

RCT Randomised controlled trial; *FS* Febrile seizure
Study number 3 and 6 had used the same sample. Study 15 and 17 used the same sample. Study 16 used the reference group of 15 plus a new cohort.
[a] Study 8 included 14 previous studies: 3 population-based studies, 3 cohort studies, 4 RCT's and 4 hospital-based studies. In study 8 had been included study 1-7.
[b] Study 11 included 5 previous studies, of which the individual patient data were analysed: 2 cohort studies and 3 hospital-based studies. Study 11 included study 2,3,6,7 and 10.

was also associated with a recurrence. In accordance with one other study high temperature at fever onset and throughout the fever episode (measured each six hours) also predicted a recurrence in our data.[85]

Inclusion	Informed consent	Outcome	Statistics
Initial FS, unselected	unknown	First recurrence	Life table method
Initial FS, unselected	unknown	At least one recurrence	Logistic regression
Initial FS, unselected	yes	First recurrence	Cox regression
Initial FS, unselected	unknown	At least one recurrence	Chi-square
Initial FS, unselected	unknown	At least one recurrence	Cox regression
Initial FS, unselected	yes	First recurrence	Cox regression
Initial FS, unselected	unknown	First recurrence	Chi-square tests
Initial FS, unselected	unknown	1.First recurrence 2.Subsequent recurrences	Metaanalysis-techniques
Initial FS, unselected	yes	First recurrence	Cox regression
Initial FS, unselected	unknown	At least one recurrence	Cox regression
Initial FS, unselected	in one study:yes	1.First recurrence 2.Any recurrence	Cox regression
Initial FS, unselected	yes	At least one recurrence	Logistic regression
Initial FS, unselected	yes	First recurrence	Cox regression
Initial FS, unselected	yes	1.First recurrence 2.Subsequent recurrences	Cox regression
Any FS, high recurrence risk	yes	First recurrence after study entry	Cox regression
Any FS, high recurrence risk	yes	First recurrence after study entry	Logistic regression
Any FS, high recurrence risk	yes	First recurrence after study entry	Poisson regression

Important risk factors for seizure recurrence

Some important predictors of febrile seizure recurrence found in several large studies did not predict seizure recurrence in our study population. We give several possible explanations.

According to Table 8.2 the 'known' risk factors for febrile seizure recurrence have been verified in several studies, including one large sample of 2496 children who had participated in five different follow-up studies.[83] In this pooled analysis individual patient data were analysed. Four of the five studies had separately previously assessed that similar risk factors were associated with febrile seizure recurrence.[74,76,79,82] Earlier a metaanalysis was performed

including 14 previous studies and a total of 4414 cases.[80] Because of the relative small sample size (n=230) of our study (number 15) it is most likely that the power has been too limited to define all 'known' risk factors. Young age at initial seizure was the most important risk factor based on previous studies. This may be the reason that we found this factor associated with recurrence. Absence of associations in our data may not be interpreted as a lack of importance of the other 'known' risk factors. As shown in Table 8.2 we have included children with febrile seizures regardless of the number of febrile seizures they had suffered. They only had to have an increased risk based on high-risk inclusion criteria. If also children with a lower recurrence risk had been included, the other 'known' risk factors might have been found associated with seizure recurrence. Table 8.4 shows the frequency of the risk factors present in the sample. Selection based on high risk criteria reduces the power of the study to identify these criteria as high risk factors. Further, we studied the first seizure after study entry and have not studied risk factors of more than one seizure recurrence during follow-up. This also means that follow-up has been shorter in our study. All other previous studies included only children who had an initial febrile seizure. These studies investigated the predictors of a first seizure recurrence. In addition some studies analysed subsequent recurrences resulting in the following risk factors: young age, low temperature at the initial seizure and short time lapse since the previous seizure.[80,83,86] Family history was less important in these analyses. Another explanation for finding different results may be that in two of our studies (chapter 5) we have analysed the data using a different definition of follow-up time 'at risk' compared to the literature. This was six months after a previous febrile seizure (5.1) and subsequent fever episodes (5.2), respectively.

Of all parents whose children were eligible to participate in our randomised controlled trial, 16% did not give their informed consent and thus declined study participation (Figure 4.1). Unfortunately data about the percentage of parents who refused consent to participate in the cohort study are not available. It may have been that in previous studies (Table 8.2) informed consent was asked less frequently; 7 studies did not report whether informed consent had been asked. Of the five studies that were included in the pooled analysis[83], only one study[76] reported that informed consent was asked, the others did not report whether they had asked consent.[74,79,82,87] The evidence whether or not study participation and an informed consent procedure implicate a selection with respect to prognostic factors is still conflicting.[88-94] If so, this may have contributed to a relative absence of the 'known' risk factors' association with febrile seizure recurrence. In the report of the questionnaire studies performed among the randomised controlled trial participants (chapter 3 and 7), however, we found no difference in education and profession levels compared to the national Dutch population. Besides, the risk of getting initially affected by 'febrile seizures' has never been proved to be associated with social status or parental income.[95-97]

A selection-bias with respect to inclusion in the study of a specific hospital-population is not very likely. The majority of the previous studies have been hospital-based studies as well. Moreover the Sophia Children's Hospital and the Juliana Children's Hospital both have an emergency ward which is open 24 hours per day and the level of care regarding febrile seizures is mainly basic specialist care. One of the previous studies included patients from the same source (Sophia Children's Hospital) as we used.[82] This study was also used in the pooled analysis.[83]

Table 8.3 Risk factors for first or at least one recurrence after the initial febrile seizure
Numbers are referring to the study numbers in Table 8.2

Risk factors	Significant	Not significant	Not studied
Patient characteristics			
Female gender	15	3-6,10-14,16,17	1,2,7-9
Ethnic origin	-	14,15	1-5,7-13,16,17
Day nursery care	3	6,15	1,2,4,5,7-14,16,17
Abnormal psychomotor development	1	3,6,8,9,14	2,4,5,7,10-13,15-17
Characteristics of the initial febrile seizure			
Young age:	7[a],11[b],14[a]		
Continuous	1,2,4,10,15	12,13,16,17	3,5-9
< 12 months	8	-	1-7,9-17
≤ 15 months	3	6	1,2,4,5,7-17
< 18 months	5,9	-	1-4,6-8,10-17
Temperature < 40.0 °C	7[a],9[c],10,11,14[a]	15-17	1-6,8,12,13
Short period of fever before the seizure (< 1 hour)	9,14		1-8,10-13,15-17
Complex characteristics:			
Multiple type	3,8,10,11,15,17	1,4-6,9,12-16	7
Duration ≥ 15 minutes	1,3,8	2,4-6,9-14,15[d]	7,16,17
Focal type	1,3,8	2,4-6,9-15	7,16,17
First/second family history			
Febrile seizures	3,5,6,8-12,14	13,15-17	1,2,4,7
Non-febrile seizures	2,3,6,10,11	5,8,9,12-14	1,4,15-17
Any type of seizures	4	1,8,15	2,3,5-7,9-14,16,17
Others			
Time lapse since previous seizure (< 6 months)	-	10[c],15	1-9,11-14,16,17
Number of fever episodes:			
Continuous	12,13,16	-	1-11,14,15,17
≥ 4 per year	6	-	1-5,7-17
Characteristics of subsequent fever episodes:			
Young age at a onset of fever	17	12	1-11,13-16
High temperature at onset of fever	13,17	-	1-12,14-16
High temperature during fever	13,17	12	1-11,14-16
Viral etiology of fever	-	12	1-11,13-17

[a] more than two specific age and temperature categories
[b] recurrence risk highest between 12 and 24 months of age
[c] analysed as a continuous variable
[d] characteristic studied: seizure duration ≥ 30 minutes

Table 8.4 Factors associated with febrile seizure recurrence, analysed in RCT data (chapter 4, study 15)

Risk factors	Univariable analysis		Multivariable analysis	
	HR(CI95%)	p-value	HR (CI95%)	p-value
Patient characteristics				
Female gender *90 (39%)*	1.5 (0.9-2.5)	0.08	1.7 (1.0-2.7)	0.04[a]
Origin (Caucasian) *145 (63%)*	0.8 (0.5-1.3)	0.42		
Day nursery care *88 (38%)*	0.7 (0.4-1.1)	0.13		
Characteristics of the initial febrile seizure				
Age *1.4 (1.1-1.9)*[b]	0.5 (0.3-0.8)	0.01	0.5 (0.3-0.8)	<0.01[a]
Temperature < 40.0 °C *121 (53%)*	1.0 (0.6-1.6)	0.67		
Complex characteristics:				
Multiple type *87 (38%)*	1.8 (1.1-2.8)	0.02	1.7 (1.1-2.8)	0.03[a]
Duration ≥ 30 minutes *20 (9%)*	0.6 (0.2-1.6)	0.31		
Focal type *26 (11%)*	1.6 (0.8-3.1)	0.19		
First/second family history				
Febrile seizures *59 (26%)*	0.7 (0.4-1.3)	0.25		
Any type of seizures *93 (40%)*	0.9 (0.1-1.4)	0.53		
Others				
Age at study entry *1.9 (1.4-2.5)*[b]	0.5 (0.4-0.8)	<0.01	0.8 (0.5-1.2)	0.20
Time lapse since previous seizure *0.1 (0.04-0.2)*[b]	0.4 (0.1-2.1)	0.29		
Previous recurrent febrile seizures *84 (37%)*	1.1 (0.7-1.8)	0.67		

The frequency distribution in the study sample has been given in *italics*
[a] significantly associated with febrile seizure recurrence in the multivariable model
[b] median (25-75 percentiles) in years
HR hazard ratio

We conclude that based on the studies of risk factors of febrile seizure recurrence which have been performed until now, the following factors may be described as important (in order): young age at the initial seizure, family history of febrile seizures, low temperature at the initial seizure, multiple type initial febrile seizure and short period of fever before the initial seizure. Risk factors which clearly suggest an increased risk, but which need further study in larger samples, for instance a pooled analysis or a metaanalysis, are: number of fever episodes and temperature at onset and during subsequent fever episodes. The main explanations for only finding young age at the initial seizure and multiple type initial seizure associated with a recurrence in our data and for not confirming the importance of the other 'known' risk factors are most likely the small sample size of our study, the selection based on high risk criteria, and young age being a very strong risk factor based on previous studies.

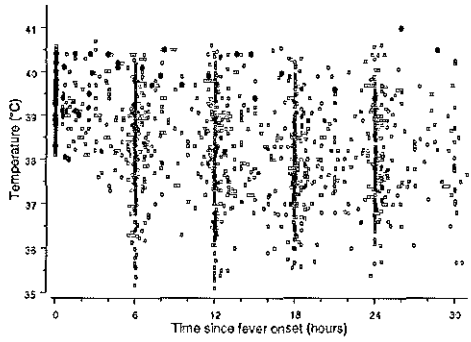

Figure 8.1 Temperature versus time since fever onset and febrile seizure recurrence (509 fever episodes). The small white boxes represent the temperature without seizure recurrence and the black dots indicate the temperature at seizure recurrence.

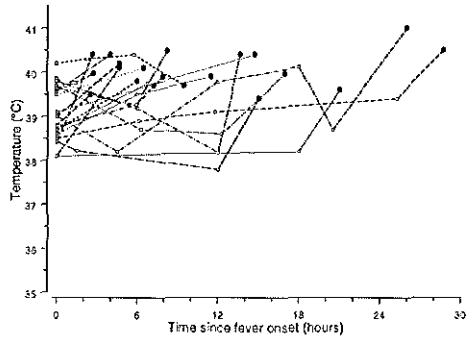

Figure 8.2 Temperature versus time since fever onset in the fever episodes accompanied by a febrile seizure recurrence between 2 hours and 30 hours after fever onset (20 fever episodes). Three recurrences occurred after 30 hours of fever. The small white boxes represent the temperature without seizure recurrence and the black dots indicate the temperature at seizure recurrence. The lines connect the temperatures in the individual patient.

8.5 Pathophysiological aspects

The 'seizure threshold theory' which implies that the higher the temperature at fever onset, the higher the risk of a seizure recurrence is supported by the results of our study. The existence of a febrile seizure temperature threshold has been suggested, based on animal studies.[98-100] Later clinical studies have demonstrated that a relatively low temperature at the initial febrile seizure is associated with an increased risk of seizure recurrence (Table 8.3). A short duration of fever before the initial seizure occurs is also a risk factor for seizure recurrence (Table 8.3).[80] Further, in a matched case-control study the height of the temperature as a characteristic of the acute illness was an independent predictor of an *initial* febrile seizure.[101] These findings may suggest the existence of such a threshold and may suggest that children with a high risk for seizure recurrence may have a lower temperature threshold above which a seizure will develop.[79,80,83,101-103] In children with a high recurrence risk the threshold may be reached more easily and thus recurrent seizures will occur more frequently. It is, however, very difficult to distinguish if either the absolute temperature itself or the rapidity of its increase is the main seizure eliciting factor. In the past hyperthermia studies have been done in animal models to investigate the association between temperature and seizures, using very frequent or continuous temperature registration and EEG-monitoring.[98-100] It was described that either the rapidity of temperature increase or the height that was reached or both were associated with the occurrence of seizures, clinically as well as in the EEG. Similar results were shown in a study of children with hyperthermia, induced by intravenous administering of typhoid vaccine.[104] As the term hyperthermia already indicates these studies were done in highly unphysiological circumstances which make extrapolation to normal human conditions impossible. The suggestion provided by the results described in chapter 5.1 that the factor 'chance' plays a role in the occurrence of a febrile seizure may also be considered suggestive for the existence of a temperature threshold in the pathophysiological mechanism of febrile seizures. This is illustrated by the frequency of fever episodes being independently associated with febrile seizure recurrence: the more frequent the child suffers from a febrile illness, the longer the time 'at risk', the higher the risk of seizure recurrence. It is unknown whether this also holds for initial febrile seizures.

We assume that whether a seizure will occur (the 'temperature threshold') may be influenced by genetic factors. Genetic aspects of febrile seizures are discussed in the next paragraph. One of the main factors playing a role in the risk of recurrent febrile seizures as defined by the present studies is the child's' age. Increasing age decreases the recurrence risk (chapter 5.2).[83] Young age at the initial febrile seizure and a short time lapse after the last previous febrile seizure have shown to be major risk factors for seizure recurrence (Table 8.3).[77,80,83] The phenomenon of febrile seizures disappears when the child grows older.[105] It might be that age modulates the temperature threshold for febrile seizures. We have also demonstrated that the influence of age on febrile seizure recurrence is highly associated with the number of febrile illnesses (chapter 5.1). This may suggest that environmental factors such as infectious diseases also play a role in the pathophysiology of febrile seizures. Despite this result, however, we consider age as one of the main factors influencing the susceptibility for febrile seizures.

To determine whether an individual seizure temperature threshold exists we should frequently measure the temperature in children with recurrent febrile seizures. An individual fever pattern in relation to seizure recurrence may be present. The individual pattern may contain, for example, that whenever a seizure recurrence occurs, it occurs in the first hours after the onset of fever. Age might change this pattern. For frequent temperature measurements an easily applicable infrared tympanic thermometer can be used. This allows a safe, reliable and relatively comfortable body temperature measurement.[106-108] If such an individual pattern does not exist the results may be considered suggestive for an infectious cause or other exogenous factor playing a role in the development of a seizure.

It would be interesting to monitor the child electroencephalographically (EEG) during fever. We started a pilot study in children for EEG measurements during fever in September 1995 in collaboration with the Department of Clinical Neurophysiology. We aimed to assess the frequency of abnormal EEG-phenomena during the first hours of fever. The hospital ethical review board approved the protocol. The children participated in the randomised trial of ibuprofen to prevent recurrent febrile seizures. At fever onset we performed an standard-EEG as soon as possible (at least within two hours after fever onset). The rectal temperature was assessed at the onset of the EEG-registration. The registration took one hour on average and was only carried out during daytime. Only five parents gave informed consent for the EEG during fever of their child. The refusing parents did not want to subject their feverish child to the investigation. All five children had a fever (≥38.5 °C) at EEG-registration onset. We found no EEG-abnormalities. This study was terminated after one year because the inclusion rate was very low. This pilot illustrates that EEG-registration during fever in children with febrile seizures does not appear to be feasible.

8.6 Genetics of febrile seizures

Evidence about genetic factors predisposing for febrile seizures has been provided by several previous studies.[81,83,84,109-112] The most important argument of a genetic predisposition has been provided by two studies showing that febrile seizures are most likely to occur with a frequency of 10% in families where there is already a documented history of febrile seizures compared to 4% in the general population.[113,114] This may suggest a mode of inheritance according to a polygenic multifactorial threshold model. The mode of inheritance, however, is still unclear: polygenic, autosomal dominant and autosomal recessive all have received some support.[115-117]

We have studied the two candidate genes on chromosome 20q and 8q linked to Benign Familial Neonatal Convulsions (BFNC) (chapter 6.2).[118-123] One previous febrile seizures study has suggested a linkage with febrile seizures of the same locus on chromosome 8q.[124] A previous genetic study of febrile seizures performed in the Sophia Children's Hospital showed no linkage of chromosome 20q and 8q with febrile seizures.[125] These two studies investigating gene localisations for febrile seizures have used linkage analysis to study a large multi-generation family with multiple affected subjects.[124,125] We have three motives to use the

affected sib pair method instead. Large families with multiple affected subjects are not frequently available in febrile seizures.[124] In the Sophia Children's Hospital only one large family was suitable for a linkage study of febrile seizures these last five years.[125] Further, the affected sib pair method allows us to limit the study to affected pairs that have been diagnosed recently, which is important because 'febrile seizure' is a clinical diagnosis. In most cases the diagnosis is based on the history told by the parents. Linkage studies of multi-generation families will have difficulties in assessing the diagnosis because detailed information is only available for the younger generations.[124,125] The third reason is that the affected sib pair method has proved to be robust in that it is effective under circumstances of localising genes for genetically heterogeneous disorders in ethnically diverse populations as are febrile seizures.[126]

The results of chapter 6.2 showed no linkage of febrile seizures with loci on chromosome 8q and 20q. A slight non-significant suggestion of linkage on chromosome 20q was present in the non-Caucasian sample. This sample consisted of 12 families from a varied ethnic origin. Thus this suggestive observation was based on a limited number of informative families and remains to be confirmed. Each non-Caucasian family contributed approximately equally to the results; no single family had paid a relatively large contribution to the slight suggestion of linkage on chromosome 20q. This reduces the probability that the suggestion for linkage of febrile seizures with the locus flanked by marker D20S1085 is based on the presence of a gene locus for febrile seizures. The results of the exclusion analysis of chromosome 20q in the Caucasian sample confirmed that linkage to this area on chromosome 20q of febrile seizures is very unlikely. Accordingly, linkage to chromosome 8q showed to be unlikely. One other study of an extended family with febrile seizures which has been published recently excluded linkage to the chromosome 8q locus.[127] This study did not investigate the involvement of loci on chromosome 20q in febrile seizures.

There is little evidence in our study that the loci on chromosome 8q and 20q involved earlier in febrile seizures and BFNC play an important role in the occurrence of febrile seizures in the general population. Further searching of the genome will be necessary to identify genes involved in febrile seizures. To increase the power of the present study to detect linkage the sample size of the study population needs to be enlarged. Recently provided evidence for an autosomal dominant gene for familial febrile seizures on chromosome 19p requires confirmation in other families with febrile seizures, including ours.[127] In addition, given the findings on the role of potassium channels in BFNC further research may be targeted towards these channels.[122,123,128,129]

Specific phenotype subgroups may help in localising genes predisposing for febrile seizures. According to the results described in chapter 6.1 the phenotype consisting of complex characteristics of initial febrile seizures may not be helpful. Previous studies have found association between the phenotype of frequent febrile seizure recurrences and familial febrile seizures.[76,82,83,109] We will perform additional analyses using the frequency of seizure recurrences as a weighing factor to increase the likelihood of localising a gene in familial febrile seizures.

Localising genes for febrile seizures may not directly result in implications for preventive treatment of febrile seizures. Insight in the pathophysiologic basis of febrile seizures and,

possibly, of seizure disorders in general may become available when studying the genetic basis of febrile seizures.

8.7 Ethical aspects of pediatric research

Pediatric research

These last decades increasing attention has been paid to the protection of participants in clinical research. Legal and ethical aspects of clinical research in children have been frequently addressed in the international literature.[130-136] Currently national Dutch legislation is about to permit non-therapeutic clinical research in children.[137-140] An overview of the debate previous to this proposal has been published.[141] The main issue has been whether or not an individual child has to gain benefit from study participation or study results. The main motive, however, for clinical research to be permitted and performed in children is that as a group they have an equal right to benefit from scientific knowledge as adults have.[141,142] If non-therapeutic clinical research in children is prohibited children are exposed to unknown risks and normal physiology and pathophysiology in children may remain largely unknown.[143-146] Main conditions for allowing studies in children are: minimal risks, minimal disadvantages (no unequal invasive, painful or uncomfortable procedures), results not obtainable by studying adults, and informed consent from the parents.[140,145,147,148] Furthermore it has been stated that a child should be withdrawn from the study when, due to study procedures, it is unduly stressed.[137,148]

In studies aiming to assess a hereditary basis of a disease, for instance the DNA study discussed in this thesis (chapter 6.2), there is no benefit for the individual participants. Disadvantages of participation in such a study include the inconveniences of a venapuncture and a (very small) risk of being told to carry a genetically determined disease. This disease may be either the disease that is studied (febrile seizures), an associated but more severe disease (in febrile seizure studies for instance a severe type of epilepsy), or a 'chance hit' (a disease unrelated to febrile seizures, for instance a hereditary type of malignancy). Consequences of serious, unexpected findings may include psychological problems and difficulties concerning insurance or selection procedures for a job. In our informed consent procedure we have discussed these risks with every parent whose family was eligible. In the informed consent form of the genetic study of febrile seizures the issue was addressed as follows: 'When the study results are known, we will acquaint you with the general final results. Your individual results will be provided to you only, if you explicitly wish so. This way we prevent you or others involved to receive information unexpectedly or unintendedly. If you wish to receive your individual results you will be referred to the Clinical Genetics Centre involved in the study.'

Despite the possible negative consequences of study participation and the few or even non-existing benefits for the participant there is evidence that people are willing to participate in research even without being adequately provided with information [149-151] and despite the costs

of time and effort.[91,93,152] The main motive of participation is the willingness to contribute to clinical science.[152,153] The general willingness to participate in clinical research has been one of the reasons mentioned in the advice to the government with respect to allowing non-therapeutic studies in children.[137] We found that the wish to contribute to clinical science was the main reason for parents to initially consent to participate in clinical research (51%) and to be willing to participate in the future (24%) (Table 7.3 and 7.6).[153]

The willingness of parents to let their child participate in clinical research may be illustrated by our data. Of all children who met the inclusion criteria of the randomised controlled trial (chapter 4) 84% (n=230) of the parents consented to participation (Figure 4.1). In the Sophia Children's Hospital and Juliana Children's Hospital 80 children with febrile seizures had a sibling who suffered from febrile seizures as well and who met the criteria for the genetic study (chapter 6). Of their parents, 68 (85%) approved to participate. The parents of 15 children with febrile seizures and an affected sibling responded to our announcement in the magazine 'Ouders van Nu'. After explaining the study 10 (67%) said to be willing to participate. The remaining 5 parents refused participation, mainly because of the necessary venapuncture. Thus high percentages of the parents gave informed consent for the randomised controlled trial (84%) and the genetic study of febrile seizure studies (85% and 67%).

Informed consent

In pediatric studies not the participant but the parents or legal representatives are asked to give informed consent. If the child is 12 to 16 years old the child has to consent as well.[140,147,154] In the USA it has been recommended that children older than 7 years of age should have the right to refrain from participation.[145,155,156] The parents should be informed about any risks and extra procedures their child has to undergo, they should know who will benefit from the study or the results and to what extent.[140,147,148] They should be offered time to consider the proposal.[140] As the main parental responsibility is taking care of their child, they will balance the pros and cons of the information provided and then decide whether or not to consent.[131] In chapter 7 we described that 75% of the parents knew why they had signed the informed consent form, while 9% thought it was for the protectional rights of the investigator and 9% did not know. Although 75% is quite a high percentage we think the other 25% should also have known that asking informed consent and signing the form is meant to protect their individual rights.[147] Attention should be paid to explaining the reason of the signature. This should also prevent that parents think they cannot withdraw their consent due to the signature.[140,147,148]

In the process of providing information to possible study participants, we make a choice between providing extensive and detailed information versus an easy-reference version with comprehensible information. The extensive informed consent information may entail every detail of the study, which could confuse the reader. It also may include specific rather negative and depressing prognostic details which occur only rarely. We prefer a clear and sufficiently short informed consent form which may not include each and every detail of the study and the disease. A main criterium may be that the information provided is sufficient to make a responsible decision whether or not to participate.[157] It should contain honest and clear information about the risks, disadvantages and inconveniences of study participation.

[147,148,154,158] Previous studies have shown that informed consent forms usually are too complex. [159-161] In chapter 7 we asked the parents how they evaluated the difficulty of the verbal and written information. Between 2 and 5%, mainly non-West European parents, thought the information was difficult to understand,. Further, we found that parents of West-European origin were more aware of the major study details. This illustrates that the information should be adjusted to the sociocultural differences among the possible participants of the study.[153,162] In the Sophia Children's Hospital general guidelines for compiling an informed consent form have been developed recently. They have been based on a survey of the available literature and the results of a questionnaire study among ethical review boards of hospitals in the Netherlands to which 75% responded.[163]

Future studies of informed consent issues in pediatric clinical research are necessary to assess the willingness of parents and children to participate. These studies may reveal further flaws in recall, comprehension and evaluation of the information provided at informed consent procedures (chapter 7). It would be interesting to interview the participating families of the affected sib pair analysis of febrile seizures (chapter 6.2) using a similar questionnaire as the one used in the informed consent study (chapter 7).

The dilemma of being physician and investigator

In our randomised placebo controlled trial of ibuprofen to prevent febrile seizure recurrence the doctor and the investigator were the same person. This means two different relationships with the patient and his or her parents.[147,164] The physician aims to serve the benefit of the patient while the investigator is responsible for the quality of the study. There are situations in which these two different roles are conflicting. This may elicit some 'ethical uncertainties' for the research-physician.

The informed consent procedure

Parents were given information about the study and were asked informed consent during their visit at the special febrile seizures outpatient clinic two weeks after a febrile seizure of their child. Although 91% of the interviewed parents felt positive about this setting, 25% also felt obliged to participate (chapter 7). Asking for informed consent while also having to treat the patient may cause an area of tension.[147] A high patient inclusion rate is beneficiary to the study, but study participation may not always mean the best treatment for each individual patient. In our study the parents may have felt pressured to participate, which is not in accordance with freely given informed consent. They may have assumed that the physician would not have asked their consent if study participation would not have been the best treatment option for their child. A suggestion for this assumption may be that only 50% of the parents in our study had been aware of the random allocation procedure. A total of 88% was aware of the use of a placebo group, including all parents who knew about random allocation (Table 7.2).

Benefit of participation

In our study parents said to appreciate the investigator being on call 24 hours a day (38%) and the extra medical care provided (37%) as an advantage of participation (Table 7.5). This appreciation may have influenced the informed consent procedure. Parents may have

consented because of these advantages and may have evaluated the other study characteristics as less important, probably because of the relatively low risk of side effects of ibuprofen and the non-invasive approach of the study procedures. For the investigator it may be tempting to stress the advantages aiming to increase the recruitment rate, while the treating physician should pay attention to possibly uneasy study procedures and the risk of negative side effects of the study medication.

Treatment evaluation

Doctors evaluate the medication they have prescribed or advised: they assess its efficacy in the individual patient. If this is not satisfactory other treatment options will be considered, which is in the interest of the patient. The investigator and the participants, however, must remain 'blind'. For the benefit of the study compliance has to be assessed. In our study we did so by asking the parents whether the medication had been taken according to the protocol and in addition the patient diary was checked. Evaluation of the treatment efficacy (reduction of fever, feeling more comfortable) might have revealed the allocated treatment. This would also have 'triggered' the parents to which of the two groups their child had been allocated. Most parents in our study, however, did not need such a triggering question. Of all parents 51% had an opinion about the medication allocated, which was based on observing the child and the temperature measurements. After finishing the study we asked the parents to what treatment group they thought their child had been allocated (Table 8.5). Parents who were certain about the prescribed treatment were more often right than the others. The child of parents who guessed placebo and of parents who did not respond had been more frequently allocated to ibuprofen. Based on these results we may hypothesise that at least 88 (49%) had been blind ('do not know' and 'no response') and at least 32 (18%) had been unblind (parents who were certain and right). We may also consider all 50 (28%) parents who were certain about the prescribed treatment as 'psychologically unblinded', because they thought they knew to which treatment group their child had been allocated and thus had behaved accordingly (Table 8.5). In general the more obvious the signs and symptoms of the medication used, the more difficult it is to keep the doctor and the patient (parent) blind. We think that in general antipyretic treatment such as ibuprofen is more than sufficiently variable in its telltale capacities to be adequately used in randomised controlled trials.

Table 8.5 Parents' opinion about treatment allocation (n=181)

Parents' opinion	Ibuprofen (n=96)	Placebo (n=85)
Certain ibuprofen (n=31)	19 (61%)	12 (39%)
Certain placebo (n=19)	6 (32%)	13 (68%)
Guess ibuprofen (n=27)	13 (48%)	14 (52%)
Guess placebo (n=16)	11 (69%)	5 (31%)
Do not know (n=58)	29 (50%)	29 (50%)
No response (n=30)	18 (60%)	12 (40%)

Placebo-group

In our randomised controlled trial participating children were not allowed to use additional antipyretic treatment. The placebo group was needed to obtain comparability of effects.[165] Use of antipyretics in the placebo group would have diluted the study results. A possible negative

effect on placebo-using children may be 'under-treatment'. They may have felt more uncomfortable because of high fever, compared to children in the ibuprofen group and, eventually also compared to children who were not participating in the study. The justification of performing our randomised controlled trial was the unknown efficacy of antipyretics to prevent febrile seizure recurrences and the generally accepted assumption that antipyretic treatment of children with febrile seizures might *provoke* recurrent febrile seizures as soon as the fever reducing effect had ceased. There is no evidence for this assumption. Thus until the study was ended it remained unknown whether or not ibuprofen is beneficiary to the patient and whether or not the placebo group had been under-treated.[147,166,167] Of the participating parents a rather high percentage (88%) had been aware of the 50% chance of being assigned a placebo (Table 7.2). Participating parents were not allowed to administer antipyretics to their child which excludes also commonly used pain reducing medications. For only 2% of the parents this was the main disadvantage of study participation (Table 7.5). The physician-investigator, however, experienced being unable to advice antipyretic-analgesic drugs a problem.

We conclude that the conflicting role of the physician-investigator remains a difficult issue. Physicians may feel guilty or even experience moral conflicts in situations in which the benefit of the individual patient differs from the benefit of the study. Real problems arise if physicians (or their departments) are financially dependent of inclusion of patients in the study.[145,168,169] The problems of having a double role are not easily solved by extra financial support in order to appoint another person for one of the two functions. Some tasks are preferably done by someone who is both the doctor and the researcher. This is especially the case in clinical research in which not the individual patient per se but the patients as a group will benefit. In such studies both knowledge about the individual patients and specific knowledge about the research project is necessary.[157] Provided that the problems to be balanced are clear and the study fulfils the criteria of research in children we think that separation of the two roles is usually unnecessary.[138,141,147,148]

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9

Summary
Samenvatting

9 Summary

This thesis presents clinical and genetic studies in children with febrile seizures. Febrile seizures have been registered prospectively in the Pediatric Department of the Sophia Children's Hospital Rotterdam since 1988. In 1994 collaboration started with the Pediatric Department of the Juliana Children's Hospital the Hague and since then registration has taken place in both hospitals. The follow-up of children with febrile seizures has been centred round an outpatients' clinic set up for children with febrile seizures.

Chapter 1 presents a survey of the literature of clinical and genetic aspects of febrile seizures. Febrile seizures are a common seizure disorder of childhood. They occur in children between 3 months and 5 years of age in association with a febrile illness, without an underlying cause of the seizure. Febrile seizures have an excellent prognosis, which is in contrast with the impact of febrile seizures on daily family life. This impact is substantial and is usually caused by extreme parental fear.

Risk factors for febrile seizure recurrence have been widely studied and include: young age at onset of febrile seizures, family history of febrile seizures, a low body temperature at the initial febrile seizure and a multiple-type initial febrile seizure. Preventive treatment of febrile seizure recurrences with antiepileptic drugs has shown to be debatable because of their ineffectiveness or the high risk of severe side effects. Intermittent treatment with diazepam has reduced the risk of side effects. Results about its efficacy, however, have turned out to be conflicting due, at least partly, to the inherent problem of the recurrent seizure being the first presenting symptom of fever. Previous studies have also addressed the possibility of antipyretics to prevent febrile seizure recurrences. None of these studies were randomised placebo controlled trials with a standardised antipyretic treatment schedule. Thus, the results were inconclusive.

The pathophysiologic basis of febrile seizures is yet unknown. There is evidence for a genetic basis, which has been provided by clinical studies. Differentiation of subgroups of phenotypes may be helpful in localising predisposing genes, such as the phenotype of frequently recurring febrile seizures, which has been shown to have a familial predisposition. Localisation of genes involved in febrile seizures remained unsuccessful until now.

Ethics of clinical research in children have widely been debated. Knowledge about the reasons for parents to permit participation of their child and their evaluation of specific study details may be considered a contribution to this debate. Further, this knowledge may lead to improved quality of the study itself.

In **chapter 2.1** a predictive model to assess the probability of normal biochemical blood test results in children presenting with a seizure associated with fever is described. The models were based on various combinations of characteristics of the history and physical examination of 203 children who visited the Sophia Children's Hospital between 1990 and 1992 with a seizure associated with fever. Normal test results of serum levels of sodium (n=115, 68%), calcium (n=149, 89%) and glucose (n=173, 100%) were reported. The prevalence of abnormal

test results was rather low and the abnormalities were outside the morbidity range. Logistic regression was used to relate the outcome (normal test results) to the clinical characteristics. The discriminative ability of the models was 'moderate' (ROC between 0.63 and 0.66).

Chapter 2.2 presents the results of the study of the diagnostic value of leukocyte counts in children with febrile seizures. We used the same data set described in **chapter 2.1**. No clear association was found between seizure duration and blood leukocytosis ($\geq 15.0*10^9$ cells/l).

In **chapter 3** parents' perceptions of fever and febrile seizures and their knowledge of them are reported. We carried out a mailed questionnaire study among the parents whose children participated in the randomised controlled trial presented in **chapter 4**. Of the 181 responding parents, 45% were afraid or very afraid of fever. Fear of fever was strongly associated with fear of recurrent febrile seizures. Parents of children with a non-West European background were more afraid. Witnessing a febrile seizure is a very frightening experience for parents. A majority thought febrile seizures to be harmful, because they appear dangerous. In 47% the parents thought that their child was dying during the initial febrile seizure. Consequences of parental fear included frequent temperature measurements (25% measured five times per day or more), sleeping in the same room as the child (24%) and remain awake at night during fever (13%). Reassuring information about fever and febrile seizures may be helpful: 21% mentioned the information provided as their reason to consider febrile seizures not harmful anymore.

In **chapter 4** the results of the randomised double blind placebo controlled trial of ibuprofen to prevent febrile seizure recurrences are presented. In this study 230 children were enrolled. They had visited one of the two participating hospitals with a febrile seizure between 1994 and 1996. They were 1 to 4 years old and had one or more risk factors for febrile seizure recurrence. They were randomly assigned to either ibuprofen syrup 5 mg per kg body weight per 6-hourly dose (111 children) or matching placebo (119 children), to be administered during fever. Median follow up time in both groups was about 1 year. The probabilities of first recurrence after study entry (2 years' Kaplan-Meier %) were 32% in the ibuprofen group and 39% in the placebo group (p=0.70). Cox regression analysis showed that the recurrence risk in the ibuprofen group was 0.9 (CI95% 0.6-1.5) times the recurrence risk in the placebo group ('intention-to-treat'). Adjustment for baseline characteristics did not affect the risk reduction estimate. A 'per-protocol' analysis, which was limited to those recurrences which occurred in the context of study medication compliance, showed similar results.

The objective of **chapter 5.1** was to assess the association between the number of fever episodes and febrile seizure recurrence. For this purpose we performed a 6 months' follow-up study of 155 children aged 3 months to 5 years with a history of a first or a recurrent febrile seizure. We used the data of 89 children who had participated in the randomised controlled trial (**chapter 4**). The other 66 children were included afterwards; they had visited one of the two participating hospitals with a febrile seizure in 1996 or 1997. The occurrence of fever episodes and febrile seizure recurrences was prospectively documented. With logistic regression analysis we studied the association between the baseline characteristics and the number of fever episodes and the outcome: a febrile seizure recurrence. We registered 260 fever episodes in which 29 children experienced one or more febrile seizure recurrences

during follow-up. We identified two factors associated with febrile seizure recurrence: number of fever episodes (OR=1.8 per fever episode) and age at study entry (OR=0.6 per year increase). In a multivariable model only the number of fever episodes remained significant.

In **chapter 5.2** the prediction of a recurrent febrile seizure during subsequent fever episodes is described. We studied the data of the temperatures, seizure recurrences and baseline patient characteristics collected at the randomised controlled trial reported in **chapter 4**. Of all children 182 had at least one fever episode during follow-up. We registered 509 fever episodes with 67 recurrences. Half of the recurrent seizures occurred in the first two hours after fever onset. These recurrences occurred at a lower median temperature (39.3 °C) than those occurring after more than two hours of fever (40.0 °C, $p<0.001$). Multivariable Poisson regression resulted in two predictors of a seizure recurrence during a subsequent fever episode: age at fever onset (RR=0.7 per year increase) and temperature at fever onset (RR=1.7 per degree increase). If we included the temperature at onset of each six hours time interval, the prediction showed to be more accurate. A chart is presented which can be used to assess the recurrence risk if age and temperature at the onset of fever are known.

The aim of the study described in **chapter 6.1** was to assess whether familial febrile seizures are associated with complex characteristics of the initial seizure. Such a familial phenotype subgroup may be helpful to study the localisation of genes predisposing for febrile seizures. In this study 51 Caucasian children with febrile seizures with one or more affected first degree relatives and 177 without an affected first degree relative were compared with respect to complex characteristics of the initial febrile seizure. They had visited the Sophia Children's Hospital Rotterdam or the Juliana Children's Hospital Den Haag between 1994 and 1996. We used logistic regression for the statistical analysis. No difference was found in the frequency of febrile status epilepticus, multiple type initial seizure and focal characteristics.

In **chapter 6.2** an affected sib-pair analysis of febrile seizures is presented. Recently, linkage of febrile seizures to markers on chromosome 8q has been suggested. In previous studies chromosome 20q and 8q have been shown to be important in Benign Familial Neonatal Convulsions (BFNC). Because of the clinical association between BFNC and febrile seizures both loci are interesting candidate regions of febrile seizures in the general population. We studied several polymorphic markers flanking the loci on chromosome 8q and 20q in 72 sib-pairs with febrile seizures. The majority of these sib-pairs had visited the Sophia Children's Hospital Rotterdam between 1988 and 1997 or the Juliana Children's Hospital Den Haag between 1992 and 1997. The remaining children were recruited by collaboration with pediatric departments of regional hospitals, general practitioners and by an announcement in a popular family magazine in 1997. In this analysis 55 of the families were of Caucasian origin and 17 were from other backgrounds including Turkey, Morocco, the Philippines and Surinam. Microsatellite markers were used to genotype the regions (D8S1132, D8S592, D8S1179, D20S1085 and D20S171). A multipoint sib-pair analysis was performed using the 'dominance variance' option. We found no significant linkage between febrile seizures and the loci studied. The maximum average number of alleles shared between affected siblings was 68% on chromosome 20q in the non-Caucasian population. This result may be considered only a slight, non-significant suggestion for linkage to this chromosome. In the Caucasian families the percentage alleles shared remained close to 50%. An exception was shown by the

analysis of chromosome 8q (58%), which was also shown by the overall analysis. An additional exclusion analysis performed in the Caucasian families showed that linkage of febrile seizures to chromosome 20q and 8q is very unlikely in this sample.

In **chapter 7** we aimed to assess the quality of the informed consent process. We sent a questionnaire to the parents of the children who participated in the randomised controlled trial presented in **chapter 4**. Some results of this mailed questionnaire were presented in **chapter 3**. The sociodemographic status of the responding parents was similar to the Dutch national distribution. On average 73% of them were aware of the major study characteristics. Their reasons for granting approval were contribution to clinical science (51%) and the benefit of their child (32%). Their perception of the informed consent procedure in the outpatients' clinic for children with febrile seizures was also assessed: 89% felt positive but 25% felt also obliged to participate. The parents experienced the investigator being on call 24 hours a day (38%) and the extra medical care and information (37%) as advantages of participation. Disadvantages were mainly the time consuming aspects and the hassle factor (23%). Interestingly, 60% of the parents were willing to participate in future studies, mainly to contribute to clinical science (24%) and for the benefit of their child and other children (18%).

In **chapter 8** we discuss the results of the previous chapters in the light of the literature. We present the conclusions for the laboratory diagnostics, treatment, prognosis and parental experience of febrile seizures and conclusions about the informed consent procedure in the randomised clinical trial.

We confirmed that routine testing of sodium, calcium and glucose is not indicated. Two specific conditions in which a glucose test is indicated have been given by the international guidelines: a still convulsing child and a prolonged postictal period. The score chart that we constructed is an additional tool to a carefully performed patient history and physical examination. It may help to decide if a biochemical test is indicated for the individual patient. In children with a low probability of a normal result as calculated by the score chart the test may be indicated. Increased peripheral leukocyte counts should not be misinterpreted as related to the seizure duration. In children with febrile seizures leukocyte counts should be used to evaluate the underlying cause of the fever.

Parental fear of fever and febrile seizures is a major problem. We suggest that information about fever and febrile seizures should be provided to all parents preferably during their contact with preventive health care providers. Parents of children with a non-West European background need information which is tailored to their language and culture.

We found no evidence that ibuprofen 5 mg per kg per six-hourly dose administered during fever in children with febrile seizures prevents recurrent seizures. We found similar results if we limited the analysis to those events which occurred in the context of study medication compliance ('per-protocol analysis'). Further studies may reveal whether this is due to the inefficacy of ibuprofen to reduce fever in those fever episodes in which a recurrence occurs. Antipyretics may be given during a febrile illness to make the child feel more comfortable. Consultation should emphasise the generally benign character of febrile seizures.

Based on the studies of risk factors for febrile seizure recurrence which have been performed until now the following factors may be described as important: young age at the initial seizure, family history of febrile seizures, low temperature at the initial seizure, multiple type initial febrile seizure and short period of fever before the initial seizure. In addition to these previously established risk factors prediction of recurrence may be more concise using the number of fever episodes and the age and temperature at onset of subsequent fever episodes. These factors may provide further suggestions for the hypothesis of a 'temperature threshold' in the pathophysiology of febrile seizures.

The familial type of febrile seizures is not likely to be associated with complex characteristics of the initial febrile seizure. Complex seizure characteristics may not be helpful in the distinction of phenotype subgroups for genetic studies of febrile seizures. We did not find evidence for linkage of febrile seizures to chromosome 8q and 20q. Further searching of the genome is necessary to localise the genes predisposing for febrile seizures. Localising genes for febrile seizures may not result in direct implications for preventive treatment. Insight into the pathophysiologic basis, however, may become available. This can help us to improve our understanding of febrile seizures and seizure disorders in general.

The informed consent procedure which we have studied functions adequately. Suggestions for improving the procedure are presented. Extra attention and information to non-west-European parents are necessary to improve parental understanding of the study involved. The main motive for parents to be willing to participate is the wish to contribute to clinical science. Measures should be taken to avoid parents feeling obliged to participate. The issue in the discussion about whether or not to permit clinical research in young children is the possible benefit for the individual child. It might be suggested that studies in children without an individual benefit should be permitted provided that some criteria are met, including parental informed consent. Ethical uncertainties of being treating physician and investigator are discussed. We think that separation of these two functions is usually not necessary.

Samenvatting

Dit proefschrift beschrijft klinisch en genetisch onderzoek bij kinderen met koortsconvulsies. Sinds 1988 worden koortsconvulsies prospectief geregistreerd op de afdeling Kindergeneeskunde van het Sophia Kinderziekenhuis Rotterdam. Vanaf 1994 vindt eveneens registratie plaats op de afdeling Kindergeneeskunde van het Juliana Kinderziekenhuis Den Haag. In beide ziekenhuizen wordt voor het vervolgen van de kinderen met koortsconvulsies een speciaal spreekuur gehouden.

In **hoofdstuk 1** wordt een overzicht gegeven van de literatuur met betrekking tot klinische en genetische aspecten van koortsconvulsies. Koortsconvulsies is een frequent voorkomende aandoening op de kinderleeftijd. De aanvallen treden op bij kinderen in de leeftijd van 3 maanden tot 5 jaar, in associatie met een koortsende ziekte, zonder dat er een onderliggend lijden voor de aanval is. De prognose van koortsconvulsies is zeer gunstig. Voor de ouders is het meemaken van een koortsconvulsie echter een buitengewoon angstwekkende ervaring, welke een aanzienlijke invloed kan hebben op het dagelijkse gezinsleven.

Er is uitgebreid onderzoek gedaan naar risicofactoren voor het optreden van recidief koortsconvulsies. De belangrijkste factoren zijn: het doormaken van de initiële koortsconvulsie op jonge leeftijd, een positieve familie-anamnese, het optreden van een initiële koortsconvulsie bij een relatief lage temperatuur, en een multipele initiële koortsconvulsie. Het behandelen van koortsconvulsies met anti-epileptica om recidief koortsconvulsies te voorkomen staat ter discussie, omdat een gunstig effect niet duidelijk is aangetoond en het risico op negatieve effecten tamelijk groot is. Intermitterende behandeling met diazepam heeft de kans op negatieve effecten verminderd, maar de resultaten over de effectiviteit ervan zijn echter niet eenduidig. Dit is waarschijnlijk mede het gevolg van het frequent optreden van recidief koortsconvulsies als eerste verschijnsel van een koortsende ziekte. De mogelijkheid om met antipyretica recidief koortsconvulsies te voorkomen is ook onderzocht. Geen van deze studies was gerandomiseerd, placebo-gecontroleerd en met een gestandaardiseerde antipyretische dosering, zodat de betekenis van de resultaten moeilijk vast te stellen is.

De pathofysiologie van koortsconvulsies is nog steeds onbekend. Klinische studies hebben aanwijzingen gegeven voor een genetische basis. De differentiatie van koortsconvulsies in verschillende fenotype-subgroepen zou kunnen bijdragen aan het lokaliseren van predisponerende genen. Een voorbeeld hiervan is het fenotype van frequent optredende recidief koortsconvulsies, waarvoor een duidelijke familiaire predispositie bestaat. Tot nu toe is de lokalisatie van genen die betrokken zijn bij het ontstaan van koortsconvulsies nog niet succesvol gebleken.

De discussie over de ethiek van klinisch wetenschappelijk onderzoek bij kinderen heeft veel stof doen opwaaien. Kennis over de beweegredenen van ouders om hun kind mee te laten doen aan klinisch onderzoek, en over de manier waarop zij het meedoen aan onderzoek ervaren, kan worden beschouwd als een bijdrage aan deze discussie. Bovendien kan deze kennis ook van belang zijn voor het verbeteren van de kwaliteit van het onderzoek zelf.

In **hoofdstuk 2.1** wordt een predictiemodel beschreven, dat kan worden gebruikt om te schatten hoe groot de kans is op een normale biochemie-testuitslag bij kinderen die zich presenteren met een convulsie bij koorts. De modellen zijn gebaseerd op verschillende combinaties van klinische karakteristieken van de anamnese en het lichamelijk onderzoek van 203 kinderen. Deze kinderen hebben vanwege een convulsie bij koorts het Sophia Kinderziekenhuis Rotterdam bezocht in de periode 1990-1992. Bij 115 (68%) van de kinderen werd een normaal natriumgehalte in het bloed gevonden, bij 149 (89%) werd een normaal calcium gevonden, en bij 173 (100%) werd een normaal glucose gevonden. De prevalentie van afwijkende testuitslagen was tamelijk laag en de gevonden afwijkingen waren mild. Met logistische regressie werden normale testuitslagen gerelateerd aan de klinische karakteristieken. Het discriminerend vermogen van de modellen was 'matig' (ROC tussen 0.63 en 0.66).

Hoofdstuk 2.2 geeft de resultaten weer van het onderzoek naar de diagnostische waarde van het leukocytengetal bij kinderen met koortsconvulsies. Dezelfde data set werd gebruikt als beschreven in hoofdstuk 2.1. Er werd geen duidelijk verband gevonden tussen duur van de convulsie en leukocytose van het perifere bloed ($\geq 15.0*10^9$ cellen/l).

Hoofdstuk 3 richt zich op de vraag hoe ouders koorts en koortsconvulsies beleven en hoe groot hun kennis hierover is. Wij hebben een enquête-onderzoek gedaan bij de ouders van de kinderen die hebben meegedaan aan de gerandomiseerde gecontroleerde studie beschreven in **hoofdstuk 4**. Van alle 181 responderende ouders was 45% bang of erg bang voor koorts. Angst voor koorts was duidelijk geassocieerd met de angst voor recidief koortsconvulsies. Ouders van kinderen met een niet-Westeuropese afkomst hadden relatief meer angst. Het meemaken van een koortsconvulsie bij een kind is een zeer angstwekkende ervaring voor ouders. Een meerderheid dacht dat koortsconvulsies schadelijk waren, omdat het er zo gevaarlijk uitziet. Van alle ouders dacht 47% dat het kind stervend was op het moment dat het de eerste koortsconvulsie kreeg. Frequent meten van de temperatuur (25% van de ouders meet vijf keer of vaker per dag), in dezelfde kamer slapen als het kind (24%) en 's nachts wakker blijven (13%) als het kind koorts heeft zijn mogelijke gevolgen van de angst van ouders. Geruststellende informatie over koorts en koortsconvulsies kan helpen: 21% van de ouders gaf aan als gevolg van de informatie die zij hadden gekregen, koortsconvulsies niet meer als schadelijk te beschouwen.

In **hoofdstuk 4** worden de resultaten gepresenteerd van de gerandomiseerde, placebo-gecontroleerde studie naar de effectiviteit van ibuprofen om recidief koortsconvulsies te voorkomen. Aan deze studie namen 230 kinderen deel. Zij bezochten tussen 1994 en 1996 één van de twee ziekenhuizen in verband met een koortsconvulsie. Deze kinderen waren 1 tot 4 jaar oud en hadden één of meer risicofactoren voor recidief koortsconvulsies. Zij werden gerandomiseerd voor ibuprofen siroop 5 mg per kg lichaamsgewicht per dosis à 6 uur (111 kinderen) of placebo (119 kinderen), toe te dienen bij koorts. De mediane follow-up tijd in beide groepen was ongeveer 1 jaar. De kans op een eerste recidief koortsconvulsie na randomisatie was 32% in de ibuprofen-groep en 39% in de placebo-groep (2 jaars Kaplan-Meier %, p=0.70). Cox regressie analyse liet zien dat de recidiefkans in de ibuprofen-groep 0.9 (CI95% 0.6-1.5) maal de recidiefkans in de placebo-groep was ('intention-to-treat').

Correctie voor baseline kenmerken veranderde deze uitkomst niet. Een 'per-protocol' analyse, waarin alleen die recidieven werden beschouwd welke optraden bij toediening van de studiemedicatie volgens het protocol, liet eveneens hetzelfde resultaat zien.

Het doel van **hoofdstuk 5.1** was om de samenhang te bepalen tussen het aantal koortsperioden dat een kind doormaakt en het optreden van recidief koortsconvulsies. Daarom werd een follow-up studie gedaan van 6 maanden bij 155 kinderen in de leeftijd tussen 3 maanden en 5 jaar. Deze kinderen hadden alle één of meerdere koortsconvulsies doorgemaakt. Voor deze studie werden de data gebruikt van 89 kinderen die hadden meegedaan aan de gerandomiseerde gecontroleerde studie (**hoofdstuk 4**). De andere 66 kinderen werden later geïncludeerd; zij hadden in verband met een koortsconvulsie één van beide ziekenhuizen bezocht in 1996 of 1997. Het optreden van koortsperioden en koortsconvulsies werd prospectief gedocumenteerd. Met logistische regressie analyse onderzochten wij de associatie tussen de baseline kenmerken en het aantal koortsperioden, en de uitkomst: een recidief koortsconvulsie. Er werden in de 6 maanden follow-up 260 koortsperioden geregistreerd, waarbij 29 kinderen één of meer recidief koortsconvulsies doormaakten. Twee factoren waren geassocieerd met het optreden van recidief koortsconvulsies: aantal koortsperioden (OR=1.8 per koortsperiode) en leeftijd aan het begin van de studie (OR=0.6 per jaar ouder). Het aantal koortsperioden bleef significant in een multivariabel model.

In **hoofdstuk 5.2** wordt de predictie van recidief koortsconvulsies in opeenvolgende koortsperioden beschreven. Wij bestudeerden de data van de temperaturen, de recidief koortsconvulsies en baseline patiëntkarakteristieken welke werden verzameld voor de gerandomiseerde, gecontroleerde studie beschreven in **hoofdstuk 4**. Van alle kinderen hadden 182 minimaal één koortsperiode tijdens follow-up. Er werden 509 koortsperioden geregistreerd met 67 recidief koortsconvulsies. De helft van de recidieven trad op in de eerste twee uur na het begin van de koorts. Deze recidieven gingen gepaard met een lagere mediane temperatuur (39.3 °C) vergeleken met de recidieven die optraden na twee uur koorts (40.0 °C, $p<0.001$). Multivariabele Poisson regressie analyse toonde twee voorspellers voor recidief koortsconvulsies in opeenvolgende koortsperioden aan: leeftijd aan het begin van de koortsperiode (RR=0.7 per jaar ouder), en temperatuur aan het begin van de koortsperiode (RR=1.7 per graad hoger). Wanneer tevens de temperatuur aan het begin van iedere 6-uurs periode werd beschouwd resulteerde dit in een betere voorspelling. Met behulp van het gepresenteerde diagram kan, als de leeftijd van het kind en de temperatuur aan het begin van de koortsperiode bekend is, gemakkelijk het recidief risico worden bepaald.

Het doel van het onderzoek dat wordt beschreven in **hoofdstuk 6.1** was om te bepalen of familiaire koortsconvulsies geassocieerd zijn met complexe kenmerken van de initiële koortsconvulsie. Een subgroep van een bepaald familiair fenotype kan van belang zijn om de lokalisatie te bestuderen van genen die predisponeren voor koortsconvulsies. In dit onderzoek werd de frequentie van complexe kenmerken van de initiële koortsconvulsie van 51 Kaukasische kinderen met een positieve eerstegraads familie-anamnese voor koortsconvulsies en 177 kinderen zonder een aangedaan eerstegraads familielid met elkaar vergeleken. Alle kinderen hadden één van beide deelnemende ziekenhuizen bezocht in verband met een koortsconvulsie in de periode 1994-1996. Met behulp van logistische regressie analyse kon geen verschil in frequentie van complexe kenmerken worden aangetoond.

Hoofdstuk 6.2 presenteert een 'affected sib-pair' analyse van koortsconvulsies. Een recente studie laat zien dat er mogelijk linkage van koortsconvulsies is met markers op chromosoom 8q. Chromosoom 20q en 8q zijn belangrijk gebleken bij Benigne Familiaire Neonatale Convulsies (BFNC). Beide loci zijn interessante kandidaat regio's voor koortsconvulsies in de algemene bevolking, vanwege de klinische associatie tussen BFNC en koortsconvulsies. Met behulp van polymorfe markers, welke dichtbij de loci op chromosoom 20q en 8q liggen, werd het erfelijk materiaal van 72 sib-pairs met koortsconvulsies bestudeerd. De meerderheid van de sib-pairs had het Sophia Kinderziekenhuis Rotterdam bezocht tussen 1988 en 1997 of het Juliana Kinderziekenhuis Den Haag tussen 1992 en 1997. De overige kinderen deden aan het onderzoek mee via kinderartsen en huisartsen uit de regio en met behulp van een oproep in een populair tijdschrift voor jonge gezinnen in 1997. Van de deelnemende families waren 55 van Kaukasische origine en 17 families hadden een andere afkomst: Turkije, Marokko, de Filippijnen en Suriname. Voor de genotypering werden de volgende markers gebruikt: D8S1132, D8S592, D8S1179, D20S1085 en D20S171. Bij de multipoint sib-pair analyse met aanname van 'dominance variance' werd geen linkage gevonden van koortsconvulsies met de bestudeerde loci. Het gemiddelde aantal allelen dat beide siblings overeenkomstig had was maximaal 68% op chromosoom 20q in de niet-Kaukasische populatie. Dit resultaat mag ten hoogste worden beschouwd als een zwakke, niet-significante aanwijzing voor linkage met dit chromosoom. In de Kaukasische families bleef het percentage overeenkomstige allelen dicht bij de 50%, met als enige uitzondering 58% bij chromosoom 8q. Dit percentage werd ook in de volledige analyse gezien. Als aanvulling werd in de Kaukasische families een exclusie-analyse verricht, welke liet zien dat in deze onderzoekspopulatie linkage van koortsconvulsies met chromosoom 20q en 8q erg onwaarschijnlijk is.

In **hoofdstuk 7** wordt het onderzoek besproken naar de kwaliteit van de toestemmingsprocedure. Wij stuurden een vragenlijst naar de ouders van de kinderen die hadden meegedaan aan de gerandomiseerde gecontroleerde studie beschreven in **hoofdstuk 4**. Een deel van de resultaten van deze enquête wordt beschreven in **hoofdstuk 3**. De sociodemografische status van de responderende ouders was vergelijkbaar met die van de verdeling in de Nederlandse bevolking. Gemiddeld was 73% van de ouders op de hoogte van de belangrijkste kenmerken van de studie. Hun beweegredenen om toestemming te geven waren: een bijdrage willen leveren aan de medische wetenschap (51%), en het voordeel voor hun kind (32%). Wij vroegen ook naar hun beleving van de toestemmingsprocedure op het speciale spreekuur voor kinderen met koortsconvulsies: 89% heef dit als positief ervaren, maar 25% van de ouders had zich ook verplicht gevoeld om mee te doen. Als voordeel van het meedoen aan de studie werd genoemd dat de onderzoeker 24 uur per dag bereikbaar was (38%), en de extra medische zorg en informatie (37%). Nadelen waren voornamelijk die onderdelen van de studie die tijd en aandacht kostten (23%). Interessant was dat 60% van de ouders opnieuw zou willen meewerken aan een vergelijkbaar onderzoek in de toekomst, met als belangrijkste reden een bijdrage te willen leveren aan de medische wetenschap (24%) en het voordeel voor hun eigen kind en andere kinderen (18%).

In **hoofdstuk 8** worden de resultaten besproken in het licht van de literatuur. De conclusies voor laboratoriumdiagnostiek, behandeling en prognose worden gepresenteerd. Ook worden de conclusies van het onderzoek naar de beleving van ouders van koortsconvulsies en van het onderzoek naar de toestemmingsprocedure in de gerandomiseerde gecontroleerde studie besproken.

Wij hebben bevestigd dat routinematige bepaling van natrium, calcium en glucose niet nodig is. Twee specifieke indicaties waarvoor een glucose bepaling geïndiceerd zijn worden gegeven in de internationale richtlijnen: een kind dat bij binnenkomst nog convulsief is, en een lange postictale periode. Het scorings-diagram is een extra hulpmiddel bij een nauwkeurige anamnese en lichamelijk onderzoek. Bij de individuele patiënt kan het behulpzaam zijn bij de afweging of een biochemisch bloedonderzoek geïndiceerd is. Bij kinderen met een lage kans op een normale testuitslag, berekend met het scorings-diagram, kan de bepaling geïndiceerd zijn. Een verhoogd leukocytengetal moet niet verkeerd geïnterpreteerd worden als een gevolg van de duur van de convulsie. Bij kinderen met koortsconvulsies kan de bepaling van het aantal leukocyten alleen gebruikt worden om de onderliggende oorzaak van de koorts vast te stellen.

Angst van ouders voor koorts en koortsconvulsies is een belangrijk probleem. Informatie over koorts en koortsconvulsies zou moeten worden gegeven aan alle ouders, bij voorkeur tijdens hun contact met de preventieve gezondheidszorg. Ouders van kinderen met een niet-Westeuropese afkomst hebben informatie nodig, welke speciaal is toegesneden op hun eigen taal en cultuur.

Wij vonden geen aanwijzingen voor een preventief effect op recidief koortsconvulsies van ibuprofen 5 mg per kg per dosis, bij koorts toegediend om de zes uur, bij kinderen met koortsconvulsies. Vergelijkbare resultaten werden gevonden wanneer de analyse werd beperkt tot die recidieven, welke optraden bij gebruik van de studiemedicatie volgens het protocol ('per-protocol analyse'). Verder onderzoek zou kunnen aantonen of dit veroorzaakt wordt door de ineffectiviteit van ibuprofen om de koorts te verlagen in die koortsperioden, waarin een recidief koortsconvulsie optreedt. Voor het comfort van het kind kunnen bij een koortsende ziekte antipyretica worden gegeven. In het contact met de ouders zou de gunstige prognose van koortsconvulsies benadrukt moeten worden.

Gebaseerd op de studies naar de risicofactoren voor recidief koortsconvulsies die tot nu toe zijn gedaan, kunnen de volgende factoren als belangrijk worden beschouwd: het optreden van de initiële koortsconvulsie op jonge leeftijd, een positieve familie-anamnese voor koortsconvulsies, een relatief lage temperatuur bij de initiële koortsconvulsie, een multipele initiële koortsconvulsie, en een korte duur van de koorts voordat de initiële koortsconvulsie optreedt. In aanvulling op deze risicofactoren kan de voorspelling van een recidief koortsconvulsie verder worden verbeterd, wanneer het aantal koortsperioden en de leeftijd en temperatuur aan het begin van de opeenvolgende koortsperioden ook in beschouwing wordt genomen. Deze factoren kunnen bovendien als ondersteuning worden gezien voor de hypothese dat er een 'temperatuursdrempel' bestaat in het ontstaansmechanisme van koortsconvulsies.

Waarschijnlijk is het familiaire type van koortsconvulsies niet geassocieerd met complexe kenmerken van de initiële koortsconvulsie. Complexe kenmerken van de convulsie zijn waarschijnlijk niet zo belangrijk bij het onderscheiden van fenotype subgroepen voor genetisch onderzoek van koortsconvulsies. Wij hebben geen aanwijzingen gevonden voor linkage van koortsconvulsies met chromosoom 8q en 20q. Om de genen te lokaliseren die predisponeren voor koortsconvulsies is nader onderzoek van het genoom nodig. De lokalisatie

van deze genen heeft waarschijnlijk geen directe gevolgen voor preventieve behandeling. Wel kan inzicht in de pathofysiologie worden verkregen, wat een bijdrage kan leveren aan het vermeerderen van onze kennis over koortsconvulsies en convulsieve aandoeningen in het algemeen.

De toestemmingsprocedure die wij hebben bestudeerd functioneert voldoende. Om de procedure te verbeteren zijn enkele voorstellen gedaan. Extra aandacht en informatie aan niet-Westeuropese ouders zijn nodig om te zorgen dat ouders de studie waarvoor hun toestemming wordt gevraagd beter begrijpen. De belangrijkste beweegreden voor ouders om mee te doen is de wens om een bijdrage te willen leveren aan de medische wetenschap. Er zouden maatregelen genomen moeten worden om te vermijden dat ouders zich verplicht voelen om deel te nemen. In de discussie over de toelaatbaarheid van klinisch onderzoek bij kinderen speelt het mogelijke belang dat het individuele kind bij deelname heeft een zeer belangrijke rol. Gesteld kan worden dat onderzoek bij kinderen zonder een individueel belang voor het kind toelaatbaar is, op voorwaarde dat voldaan wordt aan bepaalde criteria, zoals de toestemming van de ouders. Ethische dilemma's die zich kunnen voordoen wanneer een behandelend arts tegelijkertijd de functie van onderzoeker heeft worden besproken. Wij vinden dat scheiding van deze twee rollen meestal niet noodzakelijk is.

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Curriculum vitae

Margriet van Stuijvenberg was born in Hoogeveen on May 26, 1965. After completing secondary school (VWO) in 1984 she spent a year studying Biology at the University of Groningen. In 1985 she started her medical training at the University of Groningen. In 1992 she obtained her medical degree. From November 1992 until March 1994 she was a resident in paediatric surgery at the Sophia Children's Hospital in Rotterdam (Head of the department Prof. Dr J.C. Molenaar).

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In July 1998 she started her training in paediatrics at the University Hospital of Groningen (Head of the department Prof. Dr P.J.J. Sauer).

List of publications

M van Stuijvenberg, EN van Gijssel, EW Steyerberg, KGM Moons, G Derksen-Lubsen, HA Moll. Seizures associated with fever: clinical data as predictors for normal biochemical blood levels. *Eur J Pediatr 1998;157:592-598.*

M van Stuijvenberg, HA Moll, EW Steyerberg, EN van Gijssel, KGM Moons, G Derksen-Lubsen. The duration of febrile seizures and peripheral leukocytosis. *accepted for publication in J Pediatr.*

M van Stuijvenberg, S de Vos, GCH Tjiang, EW Steyerberg, G Derksen-Lubsen, HA Moll. Parents' fear regarding fever and febrile seizures. *submitted for publication.*

M van Stuijvenberg, G Derksen-Lubsen, EW Steyerberg, JDF Habbema, HA Moll. Randomized controlled trial of ibuprofen to prevent febrile seizure recurrences. *accepted for publication in Pediatrics.*

M van Stuijvenberg, NE Jansen, EW Steyerberg, G Derksen-Lubsen, HA Moll. The frequency of fever episodes related to febrile seizure recurrence. *accepted for publication in Acta Paediatr.*

M van Stuijvenberg, EW Steyerberg, G Derksen-Lubsen, HA Moll. Temperature, age and febrile seizure recurrence. *accepted for publication in Arch Pediatr Adolesc Med.*

M van Stuijvenberg, E van Beijeren, NH Wils, G Derksen-Lubsen, CM van Duijn, HA Moll. Characteristics of the initial seizure in familial febrile seizures. *submitted for publication.*

M van Stuijvenberg, P Heutink, L Testers, LA Sandkuijl, D Lindhout, G Derksen-Lubsen, CM van Duijn, HA Moll. No evidence for febrile seizures linked to genetic markers on chromosome 8q and 20q. *in preparation.*

M van Stuijvenberg, MH Suur, S de Vos, GCH Tjiang, EW Steyerberg, G Derksen-Lubsen, HA Moll. Informed consent, parental awareness, and reasons for participating in a randomised controlled study. *Arch Dis Child 1998;79:120-125.*