Febrile seizures

Familial risk factors, outcome and preventive use of antipyretic drugs

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Febrile seizures

Familial risk factors, outcome and preventive use of antipyretic drugs

Koortsconvulsies

Familiaire risicofactoren, uitkomst en behandeling met antipyretica

PROEFSCHRIFT

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Dedicated to Jesus Christ, who gave meaning to my life.

Voor mijn ouders.

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List of abbreviations

FS	: febrile seizure(s)
FSE	: febrile status epilepticus
BFNC	: benign familial neonatal convulsions
NSAID	: non-steroidal anti-inflammatory drug
C_{max}	: maximum plasma concentration of drug
T_{cmax}	: time of maximum plasma concentration of drug
$T_{1/2}$	: elimination half time
OTC product	: over the counter: without prescription drug
Temp(t)	: temperature at time t
ΔTemp(t)	: temperature difference from base-line at time t
ΔTemp(max)	: max temperature decrease from base-line
$T_{\Delta Tempmax}$	: time of maximum temperature decrease
AUC	: area under the (temperature) curve
%Red	: percentage of temperature reduction from base-line towards 37°C
RCT	: randomized clinical trial

1 General introduction

Symptomatology

Febrile seizures (FS) occur in early childhood during a febrile illness. A typical or simple FS is characterized by a sudden loss of consciousness with either stiffening and myoclonic jerking or total loss of muscle tone. During a short initial tonic phase of the seizure, the child may stop breathing and turn blue. After a clonic phase of up to approximately 10 minutes of jerking or a phase of mere flacidness, the seizure stops and consciousness is recuperated. The child may then either fall into a deep sleep or be confused and disorientated for some time.
Atypical or complex FS are either prolonged (i.e. duration longer than 30 minutes), focal, or occur multiple times within 24 hours. Usually, the febrile illness is one of the viral infectious diseases which are common in young infants.[1,2] Besides the fever, no other cause of the seizure can be found in the history, at physical examination, nor with additional laboratory investigations.

Definition

According to the National Institute of Health (NIH) Consensus Meeting of 1981, febrile seizures are defined as '...an event in childhood, usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause.'[3] This definition was applied in our study and specified as follows: firstly, the child's body temperature at seizure occurrence was 38.5°C or greater and the age was between 6 months and 6 years. Children with cerebrospinal fluid cell count above 30/mm^3 or a positive cerebrospinal fluid culture, indicating intracranial infection, were excluded. Finally, children

with abnormal electrolyte or glucose concentrations in the blood were also excluded.

Epidemiology

Between 2 and 5% of all children in Western Europe and the USA experience febrile seizures.[4-7] One study reports a slightly higher incidence in blacks than in whites.[4] Generally, the frequency in males is somewhat higher than in females.[4-7] The cumulative incidence of FS at 6 years of age in the Netherlands is 2 to 4%.[6,7] Thus, FS form the largest group of seizures in (early) childhood; the cumulative incidence of other seizures is 0.5 to 1%.[8,9]
The peak incidence of FS is between the age of one and two years.[5,6,10] Thirty percent of FS children experience recurrences at subsequent febrile episodes.[4,5,11,12] The recurrence risk is also highest when the child is between 12 and 24 months of age.[13] If the child remains free of recurrences until six months after the initial seizure, the recurrence risk decreases to 11%, and to 4% at one year after the initial seizure.[14]

Etiology

FS develop as a consequence of a excessive electrical discharges of neurons in the brain. The immediately preceding event is an elevated body temperature in a susceptible child. The exact mechanism by which an elevated core temperature is causing FS is presently far from understood. In the normal brain, there is a balance between the excitatory and inhibitatory system. It is assumed that when the body temperature of susceptible child raises above a certain threshold, this balance is disturbed, and the cerebrum reacts with a generalized discharge of neuron potentials.[15] This theory is supported by experimental research in mammals and in-vitro models.[16-18] Until now, the pathophysiological mechanisms by which the threshold may be lowered remain unclear.
In general, seizures will develop in any animal or human, on the condition that the temperature is high enough. Logically, children who develop febrile seizures probably a have lower temperature threshold for seizures. This is supported by the fact that children who convulse at a relatively low temperature have an increased

recurrence risk.[13,19] In accordance with the age attained incidence of initial febrile seizures, the seizure threshold is lowered during the first year of life, is lowest between one and two years of age, and comes to a 'normal' level again at the age of five to six years of age.[6,10] It is presumed that the pattern of this age attained susceptibility is determined by the process of growth and maturation of the brain. Partly, the age attained incidence of FS may be determined by the occurrence of childhood infections, which become increasingly frequent at this age.[20]

Familial factors play a major role in FS susceptibility; 25% of FS children have a positive first degree family history.[11,21] It is demonstrated that children of parents with a positive FS history have a higher risk of FS.[22-24] Furthermore is the risk of recurrent seizures after an initial seizure invariably increased when (first degree) relatives are affected by FS.[4,25,13] These findings are highly suggestive for a genetic background of FS. Until now, it is not clear to which extent familial aggregation of FS is genetically determined or what the nature of the genetic determinants might be. Several mechanisms of inheritance have been proposed so far.[26,27] Febrile seizures are associated with benign familial neonatal convulsions (BFNC), an autosomal dominant inherited disease in families.[28] In one study however, linkage of FS with the BFNC locus on chromosome 20q11 was excluded in 6 small BFNC families with some cases of FS.[29]
So far, the nature of the inherited factor remains unclear. EEG-studies revealed slow-wave-theta activity and spike foci in FS children, but this phenomenon was not associated with a positive FS family history.[30,31] Some authors reported immunoglobulin-subclass deficiencies in families of FS children[32,33], others did not.[34] As a working model, we assume that FS children have a CNS with a lower seizure threshold than other children.

Other, less important risk factors for the development of FS are maternal smoking and maternal illness, and day care attendance, which is probably related to increased exposition to infections.[35] Infectious agents which are specifically related to FS have not been identified, although an increased frequency of herpesvirus-6 infections has been reported.[36] In other studies however, the infections involved reflect those which were prevalent at that time in the community.[2,37]

Various possible etiologic agents have been proposed which may directly or indirectly induce FS development. Virus spreading to the central nervous system during viraemia has been hypothesized[1,38], but viral invasion of the CSF has only rarely been found.[1,39] Low levels of the inhibitory neurotransmitter GABA in CSF of FS children[40,41] , and hypozincemia during fever[42] have also been proposed to play a role in the etiology of FS. However, convincing evidence for any of these theories is absent. The various possible endogenic or exogenic agents which may lead to FS development will not further be discussed in this thesis.

By definition, fever is invariably associated with FS. Fever may be induced by various factors: infections, auto-immune processes, neoplasms, trauma's and intoxications.[43] Fever in young childhood is usually of viral origin, and is caused by the immune reaction of the body to the micro-organism. Activated inflammatory cells produce cytokines, interleucines, tumor necrosis factor and interferon. These substances are called (endogenous) pyrogens, because they lead to fever production.[44] Probably, pyrogens can pass the blood brain barrier and reach the vascular organ, which is located near the hypothalamus. The hypothalamus forms CNS prostaglandins, which activate the anterior hypothalamus. In the hypothalamus, the body temperature setpoint is elevated and the physiological response is arranged, which is of endocrine, metabolic, autonomic, and behavioral nature, and ultimately results in fever production.[44]

Fever may have beneficial effects for the infected child. In animal studies, mammals with serious infections and treated with antipyretics had higher mortality than their placebo treated controls.[45] One study in children with chicken pox, showed that use of acetaminophen delayed the time of healing of skin lesions.[46] Another study detected an increased time of nasal virus shedding and nasal symptoms with use of acetaminophen.[47] In a recent study on the other hand, the use of acetaminophen in febrile children with assumed viral infections did not prolong the duration of fever and symptoms.[48]
Most fevers in FS children are caused by viral upper respiratory tract infections. Therefore, the use of antipyretics is not likely to be a serious hindrance to the immune response involved, nor is it likely to affect the health of otherwise normal children with FS.

Diagnosis and acute management

The acute management of a child with a FS firstly consists of adequate supportive care, usually by providing a free airway, and administering of oxygen if necessary. At the same time, an ongoing seizure needs to be terminated as soon as possible. Patients are given rectal diazepam for seizure termination; phenobarbital, phenytoin or clonazepam are intravenously administered to non-responsive cases.[49] In rare instances, the child has to be given general anesthetics and needs to be intubated.
The majority of patients, however, recover spontaneously from their FS after 5 to 10 minutes. The actual attack is therefore mostly not witnessed by the physician. Whether an actual seizure occurred, has to be inferred from the account of an eye-witness of the attack, generally one of the parents. The doctor has to rely on the clinical history for the assessment of a FS. He has to discriminate between other disorders which may cause a seizure-like event in childhood, of which benign paroxysmal vertigo, night terrors, breath holding spells (cyanotic or pallid) and syncope are the most important ones.[50]

When a seizure is likely, intracranial causes have to be considered after the acute management of a FS (history, physical examination, and laboratory tests). The differential diagnosis is meningitis (either bacterial or viral), metabolic disorders, epilepsy (idiopathic), or cerebral bleeding. The doctor has to decide which laboratory investigations to perform, of which the most important are spinal fluid cell count and culture. Therefore, a lumbar puncture needs to be performed whenever a meningitis is suspected on clinical grounds.[50, 51] Thus, FS is a diagnosis by exclusion; no other cause for the seizure than the fever can be found.

Prognosis

Febrile seizure is generally a benign disease. In the neurologically normal child, FS does not result in serious neurological sequelae. Epilepsy, defined as two or more seizures without fever, develops subsequently in 2 to 4% of FS children.[12,52,53] The risk of epilepsy for a child without FS is 0.5 to 1%.[52] The risk of epilepsy is increased to 6 to 8 percent if the initial FS is complex, and if there is a positive family history of epilepsy.[12,52,53]

The main problem after a FS is recurrent seizures at subsequent febrile periods. FS recurrences occur in 30% of children who experienced a first FS.[4,11,12,21] After one recurrence, the chance of a second recurrence is increased to 50%.[14] Risk factors for FS recurrence are young age at occurrence of the first FS, a first multiple seizure, a family history of FS or epilepsy, and low temperature at the time of the first seizure.[13,54] In addition, the development of FS and recurrences have been shown to be dependent on the attained age and the number of previous seizures of the child.[13]

In one study, no difference in neurodevelopmental outcome was found between children who have recurrences and those who have not.[55] Generally, there seems to be no medical indication for prevention of FS recurrences. A thorough explanation of FS to the parents and reassurance about its benign nature is essential in the clinical management of FS. Information about the chance of recurrence and proper instruction of the use of diazepam rectioles at seizure recurrence is part of this. Nevertheless, the possibility of a recurrent seizure remains a source of anxiety to the parents. The total costs of laboratory investigations and hospital admissions can be considerable, since FS recurrences concern about one percent of the childhood population. Therefore, it is worthwhile to find a safe and effective means for the prevention of FS recurrences.

One may choose for continuous or intermittent prophylactic treatment of FS recurrences. In exceptional cases continuous prophylaxis with antiepileptic drugs may be given. Intermittent prophylaxis with diazepam orally, i.e. diazepam only during fever, is another option for prevention of FS recurrences. However, the use of anti- epileptic drugs and of diazepam for seizure prophylaxis is currently in debate.[56,57] For this reason, the possibility to reduce the risk of seizure recurrence by the use antipyretic drugs during fever is gaining interest. Fever reduction may prevent febrile seizures, because we presume that these seizures are caused by an elevated body temperature. To date, only two are published trials which evaluated antipyretic medication for intermittent recurrence prophylaxis. Camfield studied the preventive effect of antipyretic instruction in a placebo controlled study of phenobarbital. The use of additional antipyretics had no effect;

however, the antipyretic effect was not compared separately from the antiepileptic drugs.[58] One recent study, which investigated the combined effect of anticonvulsive and antipyretic medication, demonstrated no preventive effect of acetaminophen during fever.[59] Additional research on the prevention of FS recurrences by antipyretic medication has not yet been performed.

Outlines and aims

Since long FS are known to aggregate within families, but specific knowledge about the inheritance of this disorder is still lacking. In this thesis, three studies are described which were carried out for further specification of the genetic background of FS. The first two studies focus on the use of the family history for the prediction of FS. In chapter 2 the value of a FS history of all first, second and third degree relatives for the prediction of FS recurrences is investigated. Also studied is the question whether the proportion of first degree relatives affected yields a more differentiated risk assessment. In chapter 3 the risk of FS in siblings of FS children in the Dutch population is determined. Three selected risk factors are incorporated in a model to estimate the age attained risk of FS in siblings.

FS has been observed in several families with benign familial neonatal convulsions (BFNC), another childhood convulsive disorder which is inherited as an autosomal dominant trait. In chapter 4, genetic linkage between DNA markers of chromosome 8q24 and 20q11 implicated in BFNC and the expression of FS is studied in one large multigenerational FS family.

The prognosis of children with febrile status epilepticus (FSE) remains variable. We assessed the neurological outcome of children with a first FS presenting as a FSE (chapter 5). Furthermore, risk factors for the development of neurological sequelae were investigated.

Antipyretic drugs seem an attractive treatment for prevention of FS recurrence. Antipyretic drugs are frequently used and their antipyretic efficacy has been proved. They have a low incidence of side effects and are relatively safe. However, FS children have been excluded from antipyretic drug studies so far. It is frequently assumed that the use of antipyretic drugs during fever prevents FS recurrence, although no convincing evidence has been found yet. In chapter 6, the antipyretic efficacy of ibuprofen and

acetaminophen is determined in FS children. To estimate the potential prevention of FS recurrence by antipyretic treatment, the risk of recurrence of FS is compared between children offered treatment with antipyretic drugs and children who did not receive this treatment. This study is described in chapter 7.

The specific aims of this thesis are:

1. To determine the value of a family history of respectively first, second and third degree relatives for the prediction of recurrence of FS
2. To determine the risk of FS in siblings of FS children and the identification of risk factors for FS in siblings
3. To study whether genetic linkage exists between two BFNC loci on chromosome 8q24 and 20q11 respectively and FS susceptibility
4. To determine the risk and severity of sequelae after FSE and to identify the risk factors for sequelae
5. To determine the antipyretic efficacy of ibuprofen and acetaminophen in FS children
6. To estimate the potential preventive effect of treatment with antipyretic drugs during fever on FS recurrences

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PART I

FAMILIAL RISK FACTORS

Family history and recurrence of febrile seizures

2

A. van Esch, E.W. Steyerberg, M.Y. Berger, M. Offringa, G. Derksen-Lubsen, J.D.F. Habbema.

ABSTRACT

To determine the value of a detailed family history for the assessment of the risk of recurrence of febrile seizures (FS), 115 children who visited the emergency room of an academic children's hospital were studied prospectively. The recurrence risk of FS was analyzed in relation to the child's family history and the proportion of relatives affected by FS, using Kaplan-Meier estimates and Cox proportional hazard models. A first degree family history positive for FS (parents or siblings affected by FS) increased a child's two-year recurrence risk from 27% to 52%. No significant increase of recurrence risk for FS was found in children with second degree relatives (grandparents and uncles/aunts) or cousins only affected by FS. Recurrence risk was significantly correlated with the proportion of first degree relatives affected by FS: risks were 27%, 40% and 83% in children whose proportion was 0,0-0.5 and 0.5 respectively. Analysis of recurrence risk in relation to a weighted proportion, adjusted for the attained age and sex of first degree relatives, showed similar results. It is concluded that application of the proportion of first degree relatives affected by FS generates a more differentiated assessment of the recurrence risk of FS.

Introduction

The cumulative incidence of febrile seizures (FS) in children in European countries is between 2 and 5%.[1-3] On average, 30% of children have a second FS and 15% have two or more recurrences after their initial FS.[3-7] Although many workers advocate prophylaxis for the recurrence of FS, controversy exists about the treatment of choice.[8-12] Moreover, it is still not possible to discriminate between children who will and children who will not have a recurrence. Further improvements in the ability to predict the recurrence of an FS will aid doctors in choosing the appropriate prophylactic treatment, if any.

A first degree family history positive for FS has been shown to be a major risk factor for recurrence of an FS in several studies; other

risk factors are young age at onset, multiple initial seizures and relatively low temperature at the initial seizure.[4-7,13] The recurrence risks for FS have been reported in relation to the presence of first degree relatives (parents and siblings) affected by FS or in relation to the presence of affected relatives of any degree.[3,14,15] The predictive value of the presence of affected second and third degree relatives on FS recurrence risk is unknown. Also, the number of a child's relatives has not so far been taken into account. In general, a child's chance of having a family history positive for FS will be proportional to the number of relatives. Thus, children with larger families will be more likely to have a positive family history.[16] An incorporation of the number of relatives in the family history of FS may yield a more accurate assessment of a child's recurrence risk.

We investigated the association between the recurrence of FS and the presence of affected first degree relatives and the presence of affected second (grand parents, uncles/aunts) or third degree (cousins) relatives separately. We also investigated FS recurrence in children in relation to the proportion of first degree relatives affected.

Patients and methods

In an ongoing prospective clinic-based follow-up study 142 consecutive children with an initial FS at between six months and six years of age were included. They attended the emergency room of the Sophia Children's Hospital/Academic Hospital of Rotterdam between February, 1988 and February, 1990. Febrile seizures were defined in accordance with the National Institute of Health consensus statement.[17] Fever had to be validated at home or in the hospital as a rectal temperature of 38.5°C or more within a period of two hours before until two hours after seizure occurrence. A recurrence of febrile seizure was defined as a subsequent febrile seizure during a new febrile period. Age at onset, gender, parental country of origin, seizure type (duration, generalization, multiplicity), temperature at onset and first degree FS family history were recorded on standardized forms at the first visit. Children with remaining neurological damage or subsequent afebrile seizures (three children) and children given continuous prophylaxis (phenobarbitone or sodium valproate) for more than three months (14 children) were excluded, leaving a study group of 125.

Parents were asked to report FS recurrences to the investigators. FS recurrence histories were ascertained at follow up visits to the clinic by one of the authors (M. Offringa). Recurrence dates and characteristics were recorded on standardized forms. Subsequent to a mailed announcement at two years after the initial FS, one investigator (A. van Esch) contacted the parents by phone to obtain complete recurrence ascertainment. The parents of 10 children could not be contacted. Of the remaining 115 children, a detailed history of all first degree relatives (parents and siblings), i.e. birth date, sex and seizure history (febrile or not, date, cause), was obtained from the parents.

Also, in West European children a detailed history was obtained of all second degree relatives (grandparents and uncles/aunts) and part of third degree relatives (cousins). In non-West European children a detailed history was obtained of all first degree relatives, but only of those second and third degree relatives who were affected by FS. Detailed family history data were recorded on standardized forms. Seizures in relatives which occurred after the initial seizure of the index child were not taken into account. Where there was uncertainty about a relative's history, parents were asked to collect additional information and were contacted once more at a later date. Relatives whose FS history remained unknown were not taken into account in the analysis.

Two-year cumulative risks of one and two FS recurrences were estimated with Kaplan-Meier survival analysis. Univariate and multivariate Cox proportional hazard regression models were used to examine the effect of risk factors on the probability of subsequent febrile seizures. Hazard ratios (HR) with 95 percent confidence intervals (CIs) were computed to compare risks of different patient subgroups. The hazard ratio may be interpreted as a relative risk of recurrence.

Firstly, FS recurrence risks were analyzed in relation to the presence of FS affected relatives among first degree relatives and in relation to the presence of affected second degree relatives or cousins. Differences in the presence of FS affected relatives between children were analyzed with Pearson's χ^2 test.
Secondly, recurrence risks were analyzed in relation to the proportion of FS affected first degree relatives, excluding the index child.

This proportion was called the crude proportion of FS affected relatives and can be expressed as:

$$N_{affected} / N_{total}$$

For example, the crude proportion would be 0.33 if a child had one unaffected sibling and two parents, one of whom was affected.

Finally, risks were analyzed in relation to a weighted proportion. This weighted proportion adjusts for the lower probability of a positive seizure history in young siblings. Weights for relatives were estimated from the cumulative probability distribution of age at onset in children with febrile seizures in a population based study[1] (figure 1) – for example, a boy, 20 months of age was assigned a weight of 0.59. All parents and children of six years of age or more were assigned a weight of unity. The denominator of the weighted proportion constitutes the summated weights (W) of all first degree relatives (n), whereas the numerator constitutes the number of positive relatives ($N_{affected}$), as it is in the crude proportion. Thus, the weighted proportion of relatives affected by febrile seizures can be expressed as:

$$N_{affected} / \Sigma W_i \qquad (i=1..n).$$

A multivariate Cox proportional hazards model was used to examine the effect of family history, the crude proportion and the weighted proportion of relatives affected by febrile seizures on the probability of the recurrence of febrile seizures, adjusting for other published risk factors for the recurrence of febrile seizures.[4-7,13] These factors were age at onset (divided in three subgroups: <1, 1-2.5 and >2.5 years), seizure type (simple or multiple) and temperature at the time of the first seizure (more or less than 40°C). The effect of age on recurrence risk was analysed with the log-rank test for trend.

Results

One hundred and fifteen children were included. Sixty five were of West European origin (mainly Dutch) and 50 were of non-West European origin (mainly Mediterranean and Caribbean). Mean age at the first FS was 1.7 years. The median follow up of children without recurrences was 2.1 years; 81 (70%) were followed for more than two years. Thirty six (31%) children had one recurrence

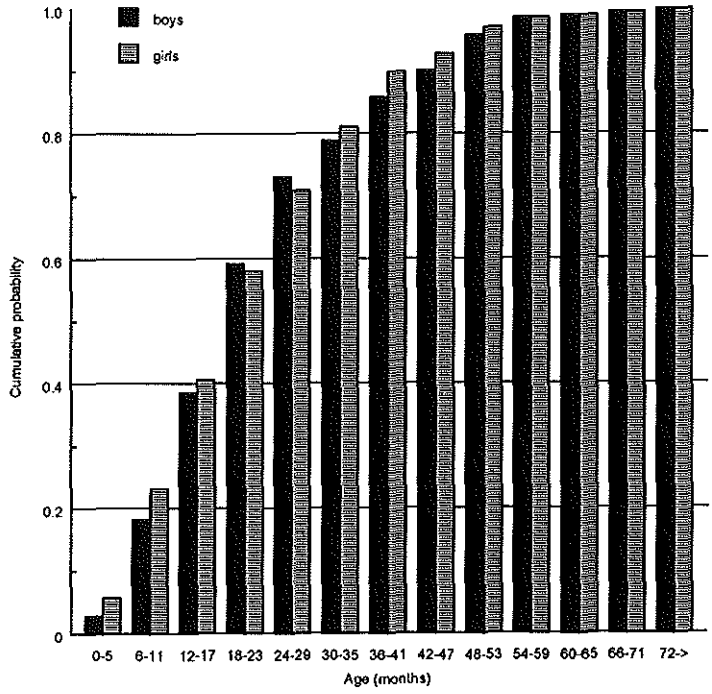

Figure 1 – Cumulative probability of having a first febrile seizure before a certain age based on Offringa *et al.*[1] The probability at 72 months is set at unity. The values are used as weights for relatives in relation to their gender and age.

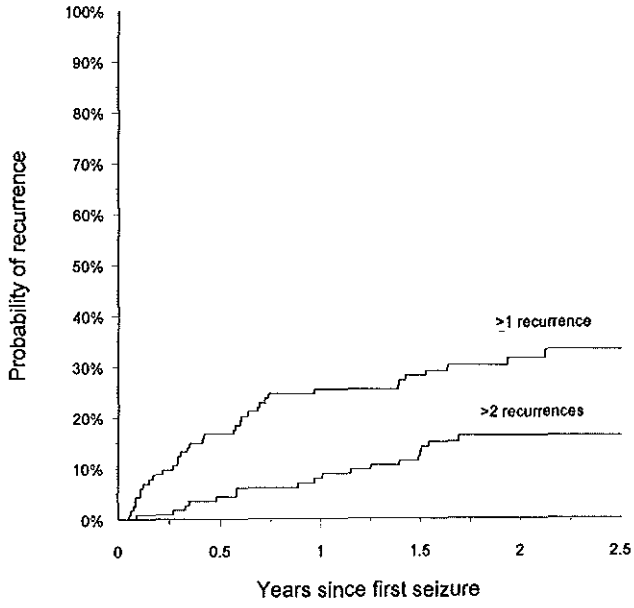

Figure 2 – Probability of one and two recurrences after first febrile seizure

Table 1 - Recurrence risks in relation to clinical characteristics

Feature	No at risk (n = 115)	No with seizure recurrence (risk*)	Hazard ratio (CI)†
Age at onset (years)			
<1	27	11 (41)	1.4 (0.7 to 2.8)
1–2.5	72	23 (32)	rc
>2.5	16	2 (13)	0.4 (0.1 to 1.5)
Gender			
Male	71	23 (35)	1.1 (0.5 to 2.1)
Female	44	13 (27)	rc
Origin of parents			
West European	65	18 (27)	rc
Non-West European	50	18 (37)	1.3 (0.7 to 2.5)
Seizure type			
Multiple	29	14 (49)	2.3 (1.2 to 4.5)
Simple	86	22 (26)	rc
Generalised	108	34 (32)	rc
Focal	7	2 (29)	0.9 (0.2 to 3.7)
≥ 15 minutes	16	8 (52)	2.3 (1.0 to 5.0)
< 15 minutes	99	28 (28)	rc
Temperature at onset			
≥ 40°C	59	13 (23)	rc
< 40°C	56	23 (41)	2.1 (1.1 to 4.1)

* Kaplan-Meier estimates (%) of two year cumulative incidence
† Univariate hazard ratios with 95% CI compared with reference category (rc)

and 18 had two recurrences. The two year risks for one and two recurrences were 31 and 16% respectively (figure 2). Table 1 gives the clinical characteristics of the 115 children with the number, percentage and hazard ratios of children with recurrences. Recurrence risks were significantly increased in children with multiple initial seizure type (HR 2.3), initial seizure duration of more than 15 minutes (HR 2.3) and relatively low temperature at the initial seizure (HR 2.1). Age at onset (p=0.07, trend test), gender and origin of parents had no significant effect on recurrence risk.

Family history of febrile seizures

A detailed febrile seizure history of 227 (total 230) parents and of 121 (total 122) siblings could be obtained. Thirteen (6%) parents and 12 (10%) siblings had had an FS. Seventeen (2.8%) of 610

Table 2 – Number of recurrences of febrile seizures, risks and hazard ratios in relation to family history of febrile seizures

		≥ 1 Recurrence			≥ 2 Recurrences		
			Hazard ratio (CI)†			Hazard ratio (CI)†	
Family history of febrile seizure	*No at risk*	*No (risk*)*	*Univariate*	*Multivariate*	*No (risk*)*	*Univariate*	*Multivariate*
None	69	19 (27)	rc	rc	10 (15)	rc	rc
2nd degree/ cousins	25	6 (24)			3 (12)		
1st degree relatives	21	11 (52)	2.5 (1.2 to 5.1)	3.2 (1.6 to 6.6)	5 (23)	2.0 (0.7 to 5.5)	2.2 (0.7 to 5.8)
All	115	36 (31)			18 (16)		

* Kaplan-Meier estimates (%) of two year cumulative incidence
† Hazard ratios with 95% CI compared with reference category (rc)

recorded second degree relatives and 12 (2.4%) of 493 recorded third degree relatives of children of West European origin had had an FS. In total, 24 second degree relatives and 20 cousins had had an FS.

Twenty one (18%) children had affected first degree relatives (table 2). Twenty five (22%) children had affected grandparents or uncles/aunts (second degree relatives) or cousins (part of third degree relatives). Risks of one and of two recurrences in children with affected second degree relatives or cousins were similar to risks of children without any affected relative. Risks of one recurrence in children with affected first degree relatives, however, were significantly increased (univariate HR 2.5 and multivariate HR 3.2). Risks of two recurrences showed a similar result (table 2).

Recurrence risks were studied in relation to the presence of affected parents or the presence of affected siblings separately. Table 3 (overleaf) shows that the recurrence risk was increased from 28% to 62% when the child had an affected parent (HR 3.1; CI 1.4-6.7). When a FS affected sibling was present the recurrence risk was increased from 29% to 55% (HR 2.4; CI 1.0-5.8). Risks of two recurrences were increased from 14% to 31% (HR 2.7; CI 0.9-8.1) and from 15% to 27% (HR 2.2; CI 0.6-7.7) respectively. Thus the presence of FS affected parents and of FS affected siblings had similar effects on recurrence risk.

Table 3 - Recurrence risks in relation to febrile seizure history of relatives

Feature	No at risk (n = 115)	No with seizure recurrence (risk*)	Hazard ratio (CI)†
No of siblings with febrile seizures			
0	103	30 (29)	rc
≥ 1	11	6 (55)	2.4 (1.0 to 5.8)
No of parents with febrile seizures			
0	101	28 (28)	rc
1	13	8 (62)	3.1 (1.4 to 6.7)
No of grandparents and uncles/aunts with febrile seizures			
0	96	31 (32)	rc
≥ 1	19	5 (26)	0.8 (0.3 to 2.0)
No of cousins with febrile seizures			
0	102	31 (30)	rc
≥ 1	13	5 (38)	1.4 (0.5 to 3.5)

* Kaplan-Meier estimates (%) of two year cumulative incidence
† Univariate hazard ratios with 95% CI compared with reference category (rc)

Recurrence risks of West European and non-West European children were studied separately because the percentage of children with FS affected first degree relatives in non-West European children (10%) was lower than in West European children (25%, p=0.04). In West European children recurrence risks were 19% in those without any affected first degree relatives and 50% in those with affected first degree relatives. In non-West European children, recurrence risks were 35% and 60% respectively. Univariate hazard ratios in children with FS affected first degree relatives were similar, that is 2.8 (CI 1.1-7.1) in West European children and 3.3 (CI 0.9-11.6) in non-West European children.

Crude proportion of relatives affected by febrile seizures

Analysis of recurrences in relation to the crude proportion of FS affected relatives showed that the risk of one recurrence increased when the proportion increased; see figure 3 and table 4. The risk of two or more recurrences was only increased in children with proportion greater than or equal to 0.5 (table 4), however.

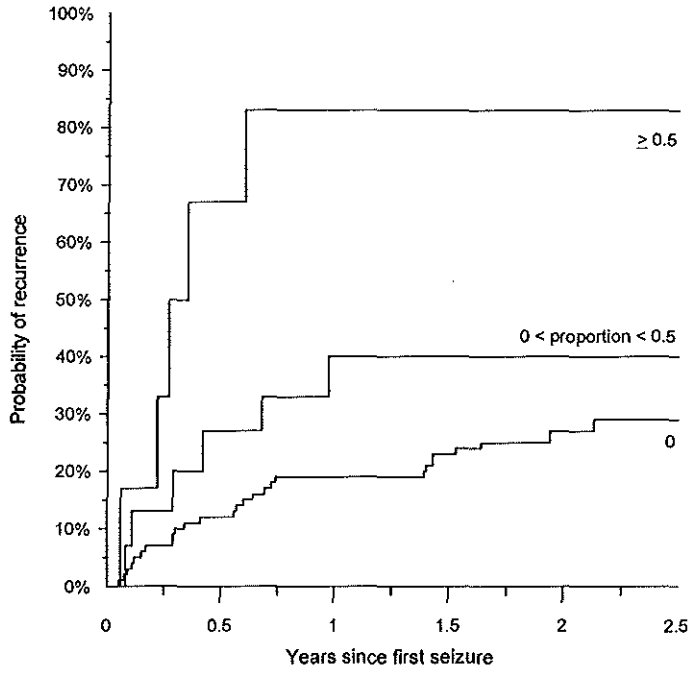

Figure 3 – Probability of recurrence in relation to the proportion of relatives affected by febrile seizures.

Table 4 –Recurrence risks for febrile seizures according to the crude proportion and the weighted proportion of first degree relatives affected by febrile seizures.

		≥ 1 Recurrence			≥ 2 Recurrences		
			Hazard ratio (CI)†			Hazard ratio (CI)†	
Family history of febrile seizure	*No at risk*	*No (risk*)*	*Univariate*	*Multivariate*	*No (risk*)*	*Univariate*	*Multivariate*
Crude proportion							
0	94	25 (27)	rc	rc	13 (14)	rc	rc
0<prop.<0.5	15	6 (40)	1.7 (0.7 to 4.1)	2.2 (0.9 to 5.6)	2 (13)		
≥0.5	6	5 (83)	6.3 (2.4 to 16.8)	6.8 (2.4 to 19.1)	3 (50)	5.2 (1.5 to 18.3)	5.7 (1.4 to 18.5)
Weighted proportion							
0	94	25 (27)	rc	rc	13(14)	rc	rc
0<prop.<0.5	13	5 (38)	1.7 (0.6 to 4.4)	2.2 (0.8 to 6.1)	2 (15)		
≥0.5	8	6 (75)	4.4 (1.8 to 10.8)	5.1 (2.0 to 12.8)	3 (47)	3.4 (1.0 to 11.8)	3.5 (1.0 to 12.5)
All	115	36 (31)			18 (16)		

* Kaplan-Meier estimates (%) of two year cumulative incidence
† Hazard ratios with 95% CI compared with reference category (rc)

Univariate hazard ratios in this group were 6.3 for one and 5.2 for two recurrences respectively, multivariate hazard ratios were 6.8 and 5.7.

Weighted proportion of relatives affected by febrile seizures

Finally, recurrence risks were analyzed in relation to the weighted proportion of FS affected relatives, which proportion is adjusted for the attained age and sex of the relatives (table 4). Although risks and hazard ratios were generally lower, the same pattern was observed as described in the crude proportion of FS affected relatives.

Discussion

The aim of this study was to determine the value of a detailed family history for the prediction of febrile seizure (FS) recurrences. In this prospective follow-up study the recurrence risks were studied in relation to the presence of FS affected relatives among first, second and a part of third degree relatives and in relation to the proportion of FS affected relatives.

Detailed family history data were obtained through interviews by phone. This method has been shown to be almost as accurate as direct interviews.[20] Therefore, we assume the accuracy of our interviews to be equivalent to that of a pediatrician's or general practitioner's interview. FS history data of second degree relatives and cousins were obtained up to two years after the initial seizure in some children, possibly introducing some recall bias. In our experience, however, very little additional information on family history becomes available after seizure recurrences. Most family information is gathered by the parents after the occurrence of their child's initial seizure. Thus the accuracy of data on the history of FS in first degree relatives will only slightly differ between children with and without recurrences.

Previous studies have shown that 90% of children's first recurrences will occur within two years of the initial seizure.[4,5,7] In this

study 35 of 36 children (97%) had their first recurrence within two years. Seventy percent of the children without recurrences were followed for more than two years.
Overall risks of one and of two recurrences in this study were 31% and 15% and are similar to recurrence risks in earlier studies.[3-7] A twofold increase of the risk of one recurrence in children with a FS affected first degree relatives was also found in other studies.[1,5-7]

In previous prospective clinic based studies 25% of all children with a first FS had a first degree FS family history.[6,21] In this study FS affected first degree relatives were present in 18% of cases. The percentage of children with FS affected first degree relatives in non-West European children (10%) was significantly lower than the percentage in West European children (25%). There is no reason to assume a lower incidence of FS in Mediterranean or Caribbean children than in West European children. More likely there has been underreporting of FS affected first degree relatives, possibly caused by reluctance to reveal FS occurrence to the investigator or by hampered access to their parents living abroad. The presence of FS affected first degree relatives yielded similar recurrence hazards in West European and in non-West European children, which is indicative of non-selective underreporting of FS affected relatives.
No significant increase in FS recurrence was found in children with FS affected second degree relatives or cousins only. So, the history FS in second degree relatives and cousins therefore appears to have little value in estimating a child's recurrence risk.

The crude proportion of FS affected relatives, being the proportion of FS affected first degree relatives, yielded much more discrimination of FS recurrence risks than common FS family history. With the use of this crude proportion children with a sixfold increased risk of one and fivefold increased risk of two recurrences could be identified, being those children of whom 50% or more of the first degree relatives were affected. Risks of two recurrences in these children were also significantly inreased. Although expected in theory, no improvement of FS recurrence risk assessment was achieved by use of the weighted proportion of FS affected relatives, with adjustment for the attained age and sex of the relatives. This may be due to the fact that two thirds (227 of 348) of first degree relatives were parents. Thus, most relatives

were no longer at risk of a FS at the initial seizure of the index children.

Both genetic and environmental mechanisms have been suggested for for the susceptibility to an increased resik of the recurrence of FS.[5,15,22-25] In our study recurrence risks for FS in children with affected siblings were similar to recurrence risks in children with affected parents. These findings support a mainly genetic mechanism, because environmental risk factors would have induced a larger effect on recurrence risk of FS affected siblings than of FS affected parents. An autosomal dominant mode of transmission can be assumed in children with proportion values of 0.5 or more. Earlier, Rich *et al* postulated an autosomal dominant mode of inheritance in children with (frequent) recurrences.[26]

We conclude that a first degree family history is of major importance in the assessment of FS recurrence risk; second and third degree family history appear to be of minor importance. The proportion of FS affected first degree relatives yields the highest differentiation of FS recurrence risk. This proportion of FS affected relatives may prove a useful tool to assess FS recurrence risk in daily pediatric practice because of the simple assessment and the uncomplicated calculation of the proportion.

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Prediction of febrile seizures in siblings; a practical approach

3

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ABSTRACT

To quantify the risk of febrile seizures (FS) in relatives of children with FS and to predict the risk of FS in siblings, we calculated cumulative risks of FS in first degree relatives of 129 children with FS. The study was conducted as a prospective follow-up study of FS recurrences at the outpatient clinic of the Sophia Children's Hospital in Rotterdam.

13 parents and 12 siblings had experienced FS, accounting for a 6-year cumulative risk of 7%. The risk of FS was increased in relatives of children with recurrent FS (12%). The risk of FS in siblings (10%) in our study was more than twice the average risk in a similar population (4%). A positive FS history in a parent, young age at onset in the proband, and recurrences in the proband were selected in a multivariable prediction model. If two or more of these risk factors were present, the risk of West European siblings to develop FS was 46% (hazard ratio 5.4).

We conclude that the cumulative risk of FS in siblings of children with FS is increased. The age attained risk of FS can be estimated using a practical model incorporating three readily available risk factors.

Introduction

Febrile seizures (FS) are known to aggregate in families. Twenty-five to 40% of FS children have a positive family history.[1,2] The genetic origin of the disease is still unknown. Linkage of FS to the genes implicated in benign familial neonatal convulsions has been excluded in one study.[3] This was confirmed in a linkage study that we performed (not yet published). Furthermore, it is still unclear to what extent FS are genetically determined.[4] For instance, there is no agreement on the proportion of patients in whom the disease is inherited nor on the mode of inheritance of FS.[2,5-7] The genetic mechanism underlying FS will be important for future molecular-biological research. For the present, quantification of the risk of FS in relatives of children with FS based on family history is clinically important. The possibility of FS in siblings is of concern to the

parents. Knowledge of the magnitude of this risk and the influencing risk factors may help doctors and parents to anticipate on seizure occurrence in their children.

In a previous study on the relation between family history of FS and FS recurrence in children, we analysed the occurrence of FS in relatives of children with FS.[8] The aim of the present study is:

1) to quantify the risk of FS in first degree relatives, and siblings in particular;
2) to identify factors which determine this risk, including the FS history of the proband and other relatives;
3) to develop a practical model to predict the risk of FS in siblings.

Methods

We conducted a follow-up study in 142 children with febrile seizures. Eligible were all consecutive patients with FS who visited the outpatient clinic of the Sophia Children's Hospital in Rotterdam between February 1988 and February 1990. A detailed description of the selection of patients, the design of the study and the collection of the data has been reported earlier.[8] For the present analysis, 3 children with remaining neurological damage or subsequent afebrile seizures and 10 patients without follow-up were excluded, leaving 129 probands. Data were collected through standardized telephone interviews with the parents on seizure recurrence in the proband and seizure history of first, second and third degree relatives. The birth date, gender and the age at seizure occurrence in relatives were recorded. The analysis reported here is limited to first degree relatives, i.e. parents and siblings.

Univariate cumulative risks of FS at six years of age in all first degree relatives and in siblings separately were estimated with Kaplan-Meier survival analysis.[9] The probands themselves were excluded from the sibling analysis. Univariable and multivariable Cox proportional hazard regression models were used to examine the effect of characteristics of the proband on the probability of FS in relatives.[10] These characteristics included gender, ethnic origin, presence of FS affected parents, number of siblings, age at the initial seizure, temperature at the initial seizure, and the presence of FS recurrences in the proband. Hazard ratios (HR) with 95 percent confidence intervals (CI) were computed to compare risks between

different subgroups. The hazard ratio may be interpreted as the relative risk of FS in relatives of patients with the characteristic compared to relatives without the characteristic. The HR is considered statistically significant if the 95% confidence interval does not include 1 ($p<.05$).
The relative importance of all proband characteristics for the prediction of FS was evaluated in a multivariable Cox model. The most relevant characteristics were selected by eliminating those risk factors from this full model that showed a very limited association with the occurrence of FS. We used the Wald test with $p=0.50$ as the limit for exclusion, arguing that most characteristics containing predictive information should be included.[11] Hazard ratios, adjusted for the presence of other factors in this model and their 95% confidence intervals were calculated.

To estimate FS risk in siblings according to their age and number of risk factors, a composite risk score for each sibling was calculated based on the findings of the selected characteristics. Origin of the parents was considered as a confounder and corrected for in the model, such that the risk estimates apply to West European children. Siblings were arranged in two risk groups, according to the presence of zero or one *or* of two or three risk factors. The cumulative probability of FS in siblings was calculated for both risk groups up to the age of six years. For newborn children, this probability denotes the six-year cumulative risk of FS. For siblings who are still unaffected at a certain age, the remaining risk of developing FS was calculated, using the cumulative probability distribution of age at the first FS in West European children as observed in a population-based study in the Rotterdam area (figure 1, overleaf).[12] This cohort provided the base-line hazard for each risk category (figure 2, overleaf). We thus assume proportionality of the age attained risk of FS in children with FS affected relatives and children in the general population.

Results

Two hundred and fifty-eight parents and 146 siblings (94 boys) of 129 probands were included in this study. 25 relatives (6.9%, 95% CI: 4.7-10) had experienced febrile seizures, 13 of these were parents and 12 were siblings. Table 1 (p. 35) shows a significantly increased frequency of FS in the families of probands with

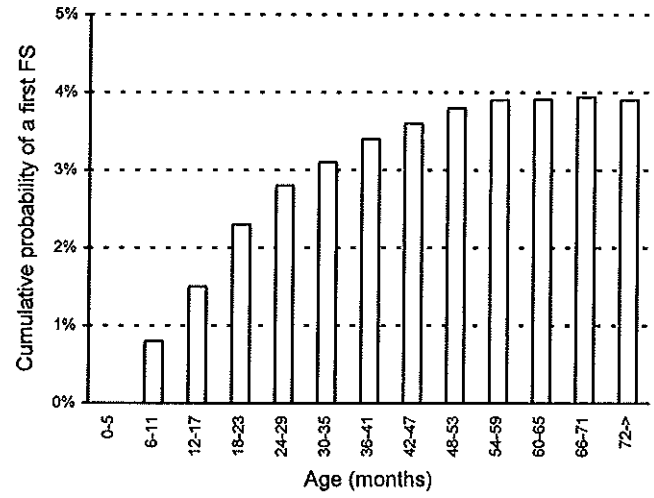

Figure 1 - Cumulative probability for children in the population of having a first febrile seizure

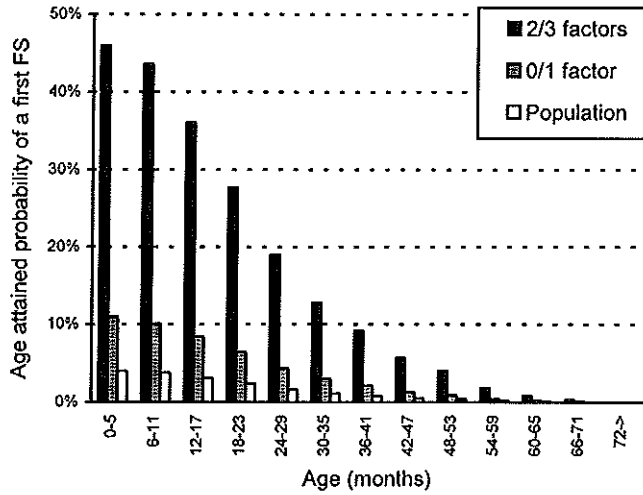

Figure 2 - Risk of a first febrile seizure in siblings, according to their attained age. Risks are given for siblings of FS children with high risk (black bars), with low risk (grey bars), and for children in the general population (white bars).

FS recurrences after the first FS (12.3%) compared to relatives of probands without FS recurrences (5.6%; HR 2.4; 95% CI 1.1-2.5). Also, there were significantly higher percentages of affected relatives of patients of West European descent (9.5%) compared to relatives of probands originating from outside Western Europe (3.3%). FS occurred in 21% of the relatives of West European probands with FS recurrences.

Overall, the frequency of FS in siblings was 10.4% (95% CI: 6.0-18). The results of the risk factor analysis in siblings were com-

Table 1 – Number of (affected) first degree relatives, risks and hazard ratios according to characteristics of the proband.

	All relatives					Siblings				
Proband characteristic	**No.**	**No. FS**	**% FS***	**HR†**	**(95% CI)**	**No.**	**No. FS**	**% FS***	**HR†**	**(95% CI)**
Gender										
Male	250	12	5.3	0.56	(0.25-1.2)	94	6	8.3	0.57	(0.18-1.8)
Female	148	13	9.5	rc	–	52	6	13.9	rc	–
Age at onset										
< 1 year	93	7	8.7	1.3	(0.56-3.2)	35	4	16.5	1.9	(0.57-6.3)
≥ 1 year	305	18	6.3	rc	–	111	8	8.6	rc	–
Temperature at onset										
< 40°C	241	17	7.9	1.4	(0.61-3.3)	85	9	14.3	2.4	(0.64-8.7)
≥ 40°C	157	8	5.4	rc	–	61	3	5.4	rc	–
Recurrences‡										
0	235	12	5.6	rc	–	97	6	7.8	rc	–
≥ 1	117	13	12.3	2.4	(1.1-5.2)	49	6	15.5	2.0	(0.65-6.3)
History of parents										
FS	–	–	–	–	–	17	3	25.4	3.1	(0.85-11.6)
No FS	–	–	–	–	–	129	9	8.7	rc	–
No. of siblings										
1	–	–	–	–	–	67	4	8.5	rc	–
≥ 2	–	–	–	–	–	79	8	11.7	1.4	(0.42-4.6)
Origin of parents										
West European	235	20	9.5	3.0	(1.1-7.9)	85	10	15.9	4.2	(0.93-19.3)
Non-West Eur.	163	5	3.3	rc	–	61	2	3.6	rc	–
All	**398**	**25**	**6.9**			**146**	**12**	**10.4**		

* Kaplan-Meier estimates of incidence of FS at six years of age
†Univariate hazard ratios with 95% CI compared with reference category
‡Probands given continuous seizure prophylaxis and their relatives were excluded

parable with the results in all relatives. A 25% incidence was found if the parents had experienced FS (table 1). Cumulative incidences were found to be highest in siblings of probands of West European descent, probands with temperature < 40°C at the initial seizure, and probands with recurrent seizures.

The factors FS history of parents (HR 1.9; 95% CI: 0.5-7.5), age at onset of the proband (HR 1.7; 95% CI: 0.5-6.1) and recurrences in the proband (HR2.5; 95% CI: 0.7-8.1) were retained in the multivariable prediction model. The hazard ratio for siblings with two or more of these risk factors was significantly increased (HR 5.4, 95% CI 1.7-17). According to the Cox model, the 6-year cumulative probability of FS in West European siblings in the low risk group (zero or one factor) was 11% at birth (95% CI 3 - 18%). The risk for a sibling in the high risk group (2 or 3 risk factors) was 46% (95%

CI 6 - 69%). The cumulative risk of FS in the Dutch population is 3.9% (95% CI 3,3-4,5%).[12]
Figure 2 shows the age attained risks of FS for siblings of FS children with low and high risk and for children in the population. A sibling in the high risk group who has remained unaffected up to the age of one year, still has a substantial risk of developing FS before the age of six years (37%, figure 2); if unaffected up to the age of two years, this risk has decreased to 20%. The risk diminishes further to 0% after the second year of life.

Discussion

We found a 7% overall risk of FS in first degree relatives of FS probands, which is comparable to the 8 to 9 percent risk found in previous studies.[5,6,13] The risk is substantially lower than expected for an autosomal recessive (25%) or autosomal dominant (50%) mode of inheritance. Findings of one other study were compatible with dominant inheritance in children with recurrent seizures.[7] We found a 16% risk of FS in siblings of probands with recurrent FS; in siblings with an affected parent, the risk of FS was 25%. These findings are compatible with other studies.[2,6,13] Only one study in Japanese children, who have a higher prevalence of FS, found a sibling risk of 45% if a parent had been affected.[2] The association of an increased sibling risk with recurrent seizures in the proband may be caused by an inherited susceptibility for febrile seizures; a polygenic mode of inheritance seems most likely. Shared environmental factors are a less plausible explanation, because an affected parent and an affected sibling equally raised the recurrence risk in the probands in our study population.[8]

The risk of FS in siblings (10.4%) in our study was more than twice the population risk (4%).[4,12] Underreporting of FS in non-West European families (3.6% risk) has to be considered; the risk in West European siblings was even 16%.[8] This last figure is similar to the risks found by others.[12,13] The susceptibilty for FS (recurrences) is determined by neuronal maturation (age, sex), exposure to infections (fever, number of sibs) and genetics (FS history of the parents); these were the risk factors investigated.[6,8,13-15] The analysis of the respective risk factors in siblings yielded results which were compatible to the results of the analysis of all first degree relatives. No statistical significance was reached

because of the small number of FS affected siblings. The factors FS history in the parents, age at onset in the proband, and FS recurrence in the proband, were selected in the prediction model. These factors have been recognised before as important for FS occurrence in siblings.[2,6] The risk of FS in siblings with two or more risk factors was significantly increased to 46% (HR 5.4, 95% CI 1.7-17). Although the classification of siblings at high risk for FS is therefore valid, the exact risk is based on small numbers. The actual risk may be lower.

The risk of FS occurrence is a function of the age of the individual child.[14] The remaining risk for an unaffected child decreases with age, both because the remaining time at risk is shorter, and because the hazard decreases with increasing age.[6] Therefore, we calculated the remaining risk from a certain age for siblings of older age. The form of this declining risk was based on the age at onset of FS of a population based cohort, providing a base-line hazard for each age.[12] The population is from the same area, and the same definition of FS and the same research group was involved, justifying the use of this procedure.

We conclude that the risk of FS in first degree relatives of FS patients was more than twice the average population risk. Recurrences in the proband was significantly associated with an increased risk of FS first degree relatives. We developed a prediction model based on three readily available characteristics that are associated with FS in siblings. From the model one can estimate the risk of a first FS in siblings of FS probands, according to their attained age. The risks can be read from figure 2 and used to inform parents of a child with FS about the risk of FS in sibling(s). This risk is markedly higher if two or three risk factors are present and diminishes to less than 10% after the age of three years.

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Febrile seizures in a large family not linked to benign familial neonatal convulsions loci on chromosomes 8q24 and 20q11

4

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ABSTRACT

A genetic background for Febrile Seizures (FS) has been suspected for several years, but no FS gene has been identified yet. As a matter of fact, the mode of inheritance is still unknown, although an autosomal dominant model has been proposed for families whose probands have recurrent FS. FS occurs frequently in children with previous Benign Familial Neonatal Convulsions (BFNC), an autosomal dominant trait in early childhood. We investigated whether genes for BFNC might be or involved in susceptibility for FS. Therefore, we performed a genetic linkage analysis in a three-generational FS family with multiple affected relatives. Markers for the chromosomal regions 8q24 and 20q11 chromosomal regions, implicated in BFNC, were tested for linkage with FS under the assumption of autosomal dominant inheritance with reduced penetrance. Linkage of FS susceptibility with reduced penetrance with the 8q24 and the 20q11 loci of BFNC with FS susceptibility was excluded in this family.

Introduction

Febrile seizures (FS) are the most common type of seizures in children. Three to five percent of children have one or more FS before the age of six years.[1,2] FS recur at a new febrile episode in about 30 percent of the FS children.[3,4] Although the general prognosis of FS is favourable, recurrent seizures are upsetting for both parents and children. The risk of epilepsy after FS is two to three times higher than in children without FS.[3,5] Also, the risk of recurrence in a child is increased if there is a positive family history of FS, and the risk is proportionally related to the number of affected first degree relatives.[6-9]

The role of genetic factors in the etiology of febrile seizures (FS) continues to be a fascinating but mainly unrevealed area. Knowledge of the precise mode of inheritance of predisposition to FS would allow identification of patients at risk for frequent FS re-

currences or epilepsy, and elucidation of pathogenetic mechanisms, which may further increase development of preventive measures.
Autosomal dominant[10], recessive[11], and polygenic[12-16] modes have been proposed until now. Rich found evidence of an autosomal dominant mode in families of probands with recurrent FS, while the segregation in families of probands with single FS was compatible with a polygenic inheritance.[14] Recently, linkage was found between benign familial neonatal convulsions (BFNC) and genetic markers on chromosome 20q11, and later also 8q24.[17,18] (A)febrile seizures were described with high frequency in some of the BFNC families, especially in the 20q11 linked families.[19-23] In one of these studies however, inclusion of relatives of BFNC probands, who had FS only, resulted in much lower LOD scores, suggesting that FS only in BFNC families probably not represents an expression of the BFNC gene defect but is due to other factors.[22]

We performed a linkage study in a large multigenerational family with an FS poband and multiple relatives with FS to investigate whether either of the two BFNC genes on chromosome 8q24 and 20q11 may be responsible for FS susceptibility.

Methods

Family history

The family was identified in a previous clinic-based follow-up study on the relation of a detailed FS family history and FS recurrences in children after an initial FS.[9] All family members whose genome was likely to give information in linkage analysis received a letter with information on the study. All gave written informed consent for participation in the study. The study protocol was approved by the Medical Ethics Committee of the University Hospital Rotterdam and Erasmus University Rotterdam. The participants noted their medical and seizure history on a standardized data form. Seizure histories were checked and supplemented by family information obtained from their first and, if necessary, second degree relatives. Furthermore, medical data were retrieved from the general practitioners of all relatives (if informed consent was given). Participants were also asked about EEGs, antiepileptic drugs and referrals due to a seizure. If applicable, additional

information was retrieved from the medical records of the specialist. Family history was also obtained from all partcipating spouses, using a standardized family history form, to detect a possible contribution to the predisposition for FS by marriage. According to the NIH definition febrile seizures are defined as an event – usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection as defined cause.[24]

Based on the information from the family and the available medical records, family members were clinically classified as affected, possibly affected or not affected by FS (see table 'Family information'; appendix II). They were classified as affected if FS was either mentioned in a medical record or by a witness within the family, such as parents, guardians, or older siblings. Relatives were classified as possibly affected when only information from a secondary source was available (younger sibling or second degree relative) and if this was positive for FS. When all available information was negative the relatives were classified as unaffected. When no information was available the individual was classified as uninformative. Family members were classified as having (had) febrile seizure(s), epilepsy, single idiopathic seizure(s), acute symptomatic seizure(s) or none of these. Epilepsy was defined as more than one afebrile seizure without a detectable cause, a single idiopathic seizure was defined as an afebrile seizure with a likely cause. An acute symptomatic seizure was defined as a seizure with evidence of a metabolic or intracranial cause.

Laboratory analysis

Blood samples were taken by venipuncture. DNA was isolated from the blood samples according to standard procedures.[25] The chromosome 20q11 marker CMM6 (D20S19) was tested by Southern blot analysis as described by Leppert et al.[17] MS617 (D20S26) was analysed on AluI digested DNA.[26] In addition, a dinucleotide repeat located in the first intron of the neuronal nicotinic acetylcholine receptor 4 subunit gene (designated CHRNA4-CA) was tested.[27] Four dinucleotide markers from chromosome 8q24 were included in the analysis: D8S198, D8S284, D8S256 and D8S274.[18] All dinucleotide markers were tested using standard PCR protocols with

one FITC labeled primer followed by analysis on an ALF automated sequencer (Pharmacia).

Statistical analysis

We performed linkage analysis using penetrance values of 50% and 70% and a gene frequency of 0.001. The chromosome 8q24 markers D8S198, D8S284 and D8S274 with inter marker distances of 19.9% and 12.4% respectively were used in a multipoint test, using the LINKMAP program from the LINKAGE package.[28] We assumed equal allele frequencies for each observed allele. On chromosome 20q11 a similar anaysis was performed using the markers CHRNA4-CA, CMM6 and MS617 with distances of 0% and 0.5 % respectively. In cases where the number of alleles caused computational problems, the marker was recoded to 3 or 4 alleles without significant loss or gain of information as checked by the program MLINK.

Results

Patients

The proband (P01) was a healthy girl, 5 years of age and from Dutch parents; gestation and delivery were uncomplicated (table 1). In her first month she was hospitalized and treated for oesophageal reflux. At the age of 15 months she had two attacks of generalized seizures, duration about 20 minutes each, during a febrile illness. She was hospitalized subsequently, but no intracranial or metabolic cause could be found. Her neurological examination and development were normal. Until her 5th birthday she had 9 more recurrent febrile seizures. Her psychomotor development and school performance remained completely normal.

In this family there were seven more cases with a clear history of FS (table 1; figure 1-A/1-B, overleaf). Three individuals had a complex initial seizure: P02, the proband's mother, and P15 had a lengthy initial seizure, and P04, brother of the proband, had a multiple initial seizure during gastro-enteritis with a subsequent sepsis (fully recovered). P15 and P29 had many recurrences up until their fifth birthday despite treatment with anti epileptic drugs

Table 1 – Clinical diagnoses, age at diagnosis and EEGs of affected persons

Individual	Diagnosis	Age at onset	EEG
P01	. multiple FS + many recurrences	1 year	-
P02	. lengthy FS	3 years	normal
	. syncope attacks		
P04	. multiple FS	1 year	normal
P06	. possibly FS	unknown	-
P08	. syncope attacks	31 years	-
P10	. FS	5 years	-
P12	. seizure after syncope	44 years	temp. foc.
	. syncope		
P15	. lengthy FS + many recurrences	5 months	normal
P21	. atypical headache attacks	33 years	normal
P24	. FS	2 years	-
P26	. possibly FS	unknown	-
P27	. FS	1 year	-
P29	. FS + many recurrences	1 year	not available
P34	. syncope attacks	12 years	-
P36	. seizure + death	6 months	-
P38	. FS	1 year	-
P39	. Spanish flu + seizure + death	6 months	-

(P15, P29). All available EEGs of the relatives with FS were normal. P06 and P25 were possibly affected, but there was no opportunity for validation by medical records or hetero anamnesis. One individual of the first generation (P36) had died after a seizure at the age of six months. No medical records were available and the cause of the seizure remained unknown. P12 developed a generalized seizure after a syncope at the age of 44 years. The first EEG revealed focal temporal spikes, two later EEGs showed only small temporal abnormalities.
Two first degree relatives of spouses had had seizures as well, which was taken into account in the linkage analysis. P38 had had a simple FS and P39 succumbed to a seizure during the Spanish flu epidemic.

Additionally, EEGs were performed in two of five individuals with (vasovagal) collapses (P02, P08, P12 and P34) or headache attacks

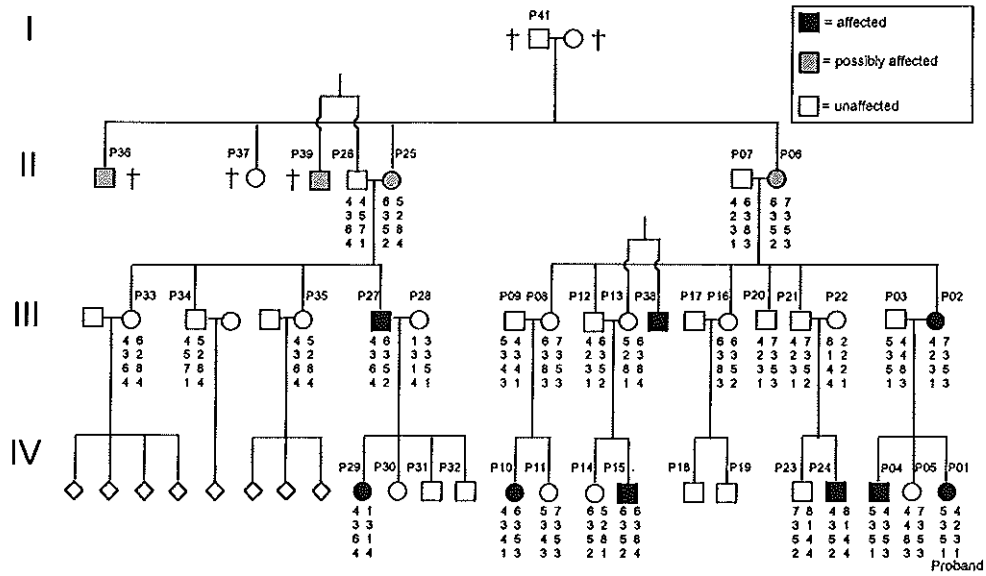

Figure 1-A – Family pedigree with chromosome 8q24 alleles.

(P21) (table1); P02 and P12 had a positive seizure history. P12 had one seizure after a vasovagal collaps. The initial EEG recording revealed temporally sharp wave activity, with later improvement. P21 suffered during a one-year period from 4 very frequent, not stress related headaches, described as atypical headache attacks. The performed EEG was normal.

Linkage analysis

This family counted 8 affected and 3 possibly affected relatives, as well as one affected and one possibly affected first degree relatives of two spouses. In total 20 meioses were available for analysis. Under assumptions of FS as a dominant trait with a reduced penetrance (50% or 70% respectively), cosegregation of BFNC markers for loci on chromosome 8q24 and 20q11 with the FS phenotype was studied.

Upon analysis of chromosome 8q24 markers, P25 and P06 (2nd generation) showed a haplotype with identical marker alleles. This haplotype was also observed in some affected individuals and obligate carriers of the third (P27, P12) and fourth (P15) generation. Part of the same haplotype may be present in P21 and P24, under the assumption of single recombination events. However,

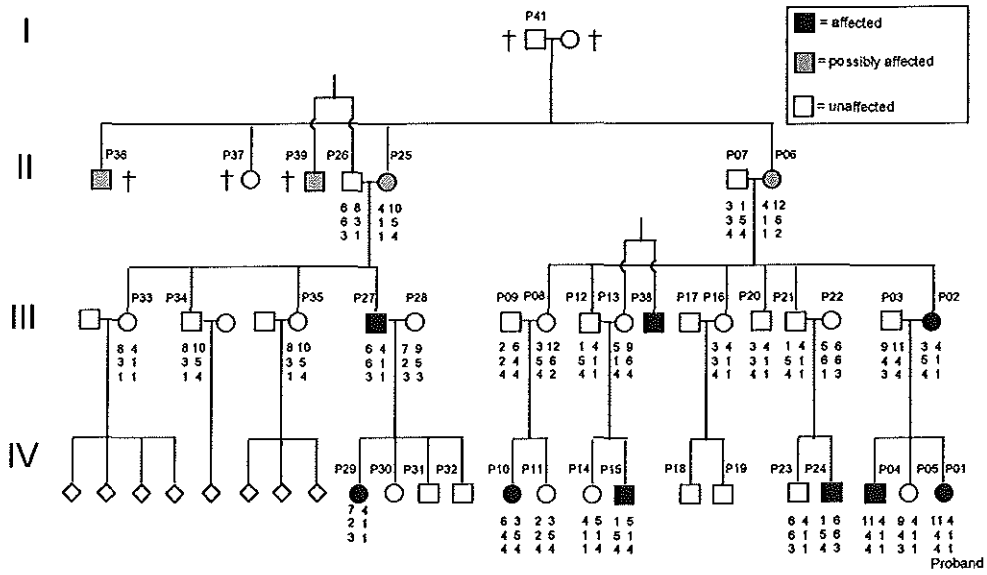

Figure 1-B – Family pedigree with chromosome 20q11 alleles.

P08 and P02 (3rd generation) most likely inherited the other haplotype from P06, and P01 (4th generation) showed the grandpaternal rather than the grandmaternal haplotype.
If we assume that the putative FS predisposing gene in the left branch of the family (P24, P27) is different from that in the right branch (P01, P02, P04, P10, P15, P24) and haplotype analysis is confined to the latter branch, also no common haplotype or marker alleles identical by descent are observed.
The LOD score for marker locus D8S284 was below -2 for the lowest penetrance assumption of 50% (figure 2, overleaf). The marker loci D8S198 and D8S274 had LOD scores of -4 and less for 50% and higher penetrance, respectively.

Also, on chromosome 20q11, P25 and P06 showed a haplotype consisting of identically sized alleles (figure 1-B). The haplotype derived from P25 was inherited by P27, who passed it on to her affected daughter P29. Both P02 and her affected offspring P04 and P01 showed the haplotype segregated by P06, but P12 and P21 did not pass it on to their affected sons. The affected status of P15 might also be explained by FS predisposing genes inherited through the spouse's mother. However, the obligate carrier P08

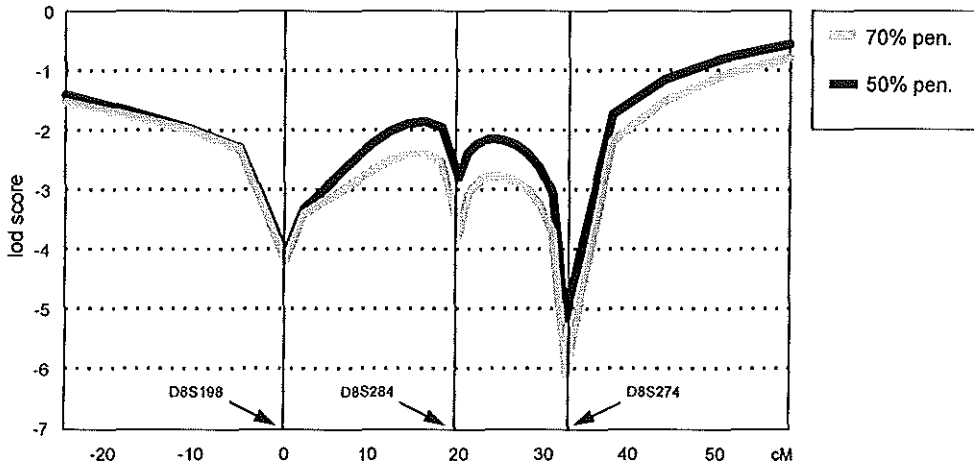

Figure 2 – Multipoint analysis for BFNC versus three markers of chromosome 8

probably received the alternative maternal haplotype and transmitted the grandpaternal haplotype to her affected daughter P10.

The marker analysis for the chromosome 20q11 loci CA and CMM6 resulted in LOD scores below -10 for linkage with FS (figure 3). The locus MS617 had LOD scores of -3 for penetrance assumptions of 50% and 70%.

Discussion

Febrile seizures (FS) are known to aggregate in families. 25 to 40% of FS children have a positive family history.[11,16] A genetic background for FS has been suspected since several years, but the mode of inheritance of the disease is still unknown.[10] Segregation analyses gave evidence of a dominant inherited factor in families with patients with recurrent FS.[14]
FS is a relatively frequent symptom in some benign familial neonatal convulsions (BFNC) families. BFNC is an autosomal dominant syndrome characterized by the onset of seizures during the first few weeks of life. No other causes of the seizures can be detected, and the children have a normal neurological development. An important observation is that several patients develop seizures later in life, which may be either febrile or afebrile.

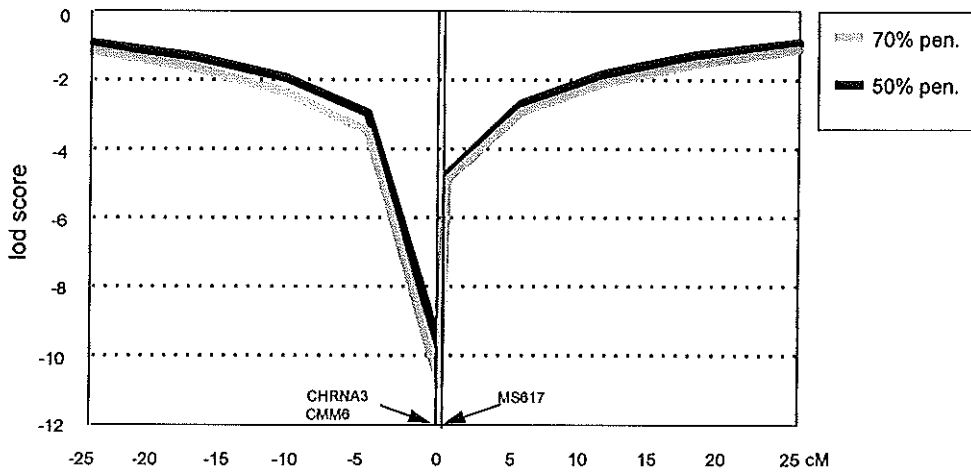

Figure 3 – Multipoint analysis for BFNC versus three markers of chromosome 20

Since 1964, more than 20 BFNC families have been identified.[17] When the neurological history between families is compared, considerable clinical heterogeneity is apparent.[19] In some BFNC families, patients have no further seizures after the first year of life. Other families however contain several patients who develop (a)febrile seizures later in life.[19] This clinical heterogeneity correlates with the results of the genetic linkage studies, which show two different marker loci for this disease. BFNC was initially localized on chromosome 20q11 by Leppert.[17] This finding was confirmed by one study in 7 small French BFNC families. In this study FS was cosegregated with FS in two patients, three patients had FS only.[22] Analysis including also patients with FS as affected, significantly lowered LOD scores, suggesting that the occurrence of FS only in BFNC families is not necessarily caused by the BFNC gene defect. Berkovic also found linkage of BFNC with chromosome 20q in a large pedigree. In this family 2 affected relatives developed FS and 1 epilepsy. Additionally, 2 unaffected relatives continued with FS and 1 with epilepsy.[23]

Genetic heterogeneity was detected by Ryan et al., who demonstrated linkage with chromosome 20q in one BFNC family, but excluded linkage with chromosome 20q in an other family.[21] The first family contained several affected relatives who had developed seizures in later life: two had developed FS, four audiogenic seizures and one epilepsy. The second family of 14 BFNC affected patients

however contained no relatives with further seizures. Additional analysis of this 'pure BFNC' family revealed linkage with chromosome 8q24.[18] Thus, there is some evidence that these two different BFNC loci are associated with clinically defined phenotypes. Against this background the question arises whether isolated FS might be linked in some families to one of the two BFNC loci.

In this study, we performed a linkage analysis on a large pedigree with multiple cases with a history of prolonged or recurrent FS. The population prevalence of FS is 2-4% in the Netherlands. Two spouses in this family had first degree relatives with FS. This was accounted for in the linkage analysis. We tested the hypothesis that the BFNC gene was responsible for FS susceptibility with reduced penetrance of 50% or 70%, as estimated from the number of obligate carriers in the pedigree. Seizure histories were validated with medical records when possible, and were cross checked with parents and with grandparents from both sides. Also, the family histories were taken from in-married spouses.

In the present study, linkage of markers for BFNC loci on chromosome 8q24 and chromosome 20q11 with the FS phenotype was excluded, in view of LOD scores of lower than -2. Thus, the BFNC genes on chromosome 8q24 and 20q11 were not responsible for FS susceptibility in this large family.

Until now, both epidemiologic and genetic studies failed to reveal a definite inheritance pattern.[10-16] Considering the FS patient population at large, a multifactorial mode of inheritance with genetic heterogeneity of major predisposing genes seems to be probable. Some major genes may be involved in families with many FS patients or with patients with FS recurrences.
Large families with multiple cases of FS, as analyzed in the present study, are seldomly available. The genetic sib-pair method investigates the number of shared alleles within affected sib-pairs at a particular marker locus.[29] Evidence for linkage between the disease locus and the marker locus is found, when the number of shared alleles is significantly greater than expected with non-linkage. Therefore, genetic sib-pair analysis may be the method for further research on the genetic background of FS.

Note — Recently, linkage was found between FS in one other family and markers for a different region on chromosome 8: 8q13-

21.[30] Additional linkage analysis was performed with markers from this region D8S533, D8S543, D8S553 and D8S579. The preliminary results of our analysis exclude linkage of these markers with FS in our family. The statistical analysis is currently being performed.

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PART II

OUTCOME

5 Outcome after febrile status epilepticus

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ABSTRACT

The neurological outcome after a first febrile status epilepticus (FSE) was retrospectively studied in 57 children. Patients were aged six to 57 months after a first seizure and had had no previous seizures or neurological abnormalities. Twelve children (24 %: 2-year Kaplan-Meier estimate) had subsequent neurological sequelae varying from speech deficit (n=9) to severe neurological sequelae and epilepsy (n=3). Speech deficit was detected after a mean period of six months. The most important predictors for sequelae were the number of different drugs needed for seizure termination and the duration of the seizure. The authors recommend that children with FSE sould be followed up for at least one year so that potential speech disorders can be detected and treated.

Introduction

Febrile Status Epilepticus (FSE) is characterized by complex febrile seizures lasting for at least 30 minutes.[1] Up to 5% of the children with febrile seizures develop FSE.[2,3] In contrast to simple febrile seizures, which have a favourable outcome, FSE can result in cerebral damage, epilepsy, and psychiatric disorders.[4-6] Several authors reported that children with prior seizures or pre-existing neurological deficits were at a higher risk of developing neurological deficits or recurrent seizures after FSE.[1,2,5] The risk of new neurological deficits was up to 50% and the risk of epilepsy up to 30%. However, children with and without pre-existing neurological deficits were presented jointly, and figures on the risk of sequelae in children with FSE were not available.

To date three studies with a small number of patients with FSE who had previously been unaffected have been published.[1,3,7] However, several children with prior febrile seizures were included in the studies. To investigate the risk of sequelae caused by FSE

we studied the outcome of first FSE in 57 children without prior neurological deficits or seizures.

Methods

Patients with FSE who had been admitted to the Sophia Children's Hospital between january 1981 and january 1991 were included. Patients were identified using the hospital record registration system, which classifies according to febrile seizures with ICD9 code 780.3.[8] The records of all children who had visited the hospital in this period due to afirst febrile seizure were reviewed. Febrile seizures were defined according to the National Institute of Health (NIH) Consensus Meeting of 1981 as '... an event in childhood, usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause' .[9] The body temperature at seizure occurrence was 38.5°C or greater and the age was between 6 months and 6 years. Patients with prior afebrile seizures or prior neurological deficits were excluded. FSE was defined as either one seizure lasting more than 30 minutes or as a series of seizures of similar duration without definite recovery in the inter-ictal phases.

Sixty-three patients were eligible. Six who were otherwise without sequelae were lost to follow-up immediately after discharge and were excluded from this analysis. Of the remaining 57 children with FSE the following characteristics were recorded: sex; age; first degree family history of seizures; whether the seizure occurred during the daytime (0600 to 1800 or at night: (1800 to 06.00); rectal temperature (<40°C or ≥40°C); cause of the fever; type of onset of the seizure (generalized or partial); duration of the seizure (≤45 or >45 minutes); number of different drugs needed to terminate the seizure (≤2 or >2); and subsequent seizure prophylaxis (specific drugs and duration). Fever work-up included a complete blood cell count with differential and platelet count; urinalysis; cerebrospinal fluid cell count and differential; bacterial cultures of blood, cerebrospinal fluid, urine, stool and throat; viral cultures of cerebrospinal fluid, nasopharynx and urine; X-ray of the thorax when indicated.

The neurological outcome at the child's last follow-up visit was evaluated. We used data from the doctor's history taking, observa-

tion and investigation in the patient record. We classified the recorded developmental disorders in the hospital records according to a screening test[10] designed to assess the developmental age of children evaluating speech, motor system, adaptive behaviour, and social contact. Hearing evaluation, if performed, was registered. Developmental disorders were classified in three categories: mild (speech development delayed six months to one year), moderate (speech development delayed one to two years), and severe sequelae (two-year speech delay or no language development, severe psychomotor defects).

The probability of detecting the developmental disorders was estimated using Kaplan-Meier survival analysis .[11] Cox proportional hazard regression models were used to compute the univariate hazard ratios (HR) of neurological sequelae with 95 % confidence intervals (CI) for sex, age, family history, time of day at seizure occurrence, temperature, seizure duration, and the number of different drugs .[12] The hazard ratio may be interpreted as a relative risk. A multivariate Cox proportional hazards model was used to examine the combined effect of correlated risk factors on the probability of sequelae.

Results

Sixty-five per cent (37) were boys. The mean age at the first occurrence of the FSE was 19 months (range 6 - 57 months). The mean temperature at seizure occurrence was 39.6°C (range 38.5°C - 40.8°C). All seizures were generalized and most started at night (58%). Causes of the fever were found in only 49%: respiratory tract infection (n=17), gastro-enteritis (n=8), exanthema subitum (n=2), and sepsis (n=1). Thirty-four patients were given diazepam rectally for seizure termination; phenytoin and phenobarbital were administered to non-responsive cases. The other 23 patients spontaneously recovered after the FSE. In 30 patients (53%), continuous treatment with phenobarbital (23 patients, in six the treatment was later changed to methylphenobarbital), methylphenobarbital (n=2) or with a combination of other agents (n=5) was started. Seizure prophylaxis was continued for a mean duration of 18 months.

Table 1 - Risks of sequelae, age and detection and follow-up time of children with neurologic sequelae

Severity of sequelae	Number with sequelae	Risk of sequelae†	Age at FSE*	Time between FSE and detection of sequelae*	Follow-up time*
Mild	5	10%	13 (11-17)	4 (1-12)	15 (11-24)
Moderate	4	9%	18 (9-46)	14 (0-41)	32 (13-55)
Severe	3	5%	13 (10-18)	0 (0 - 0)	29 (21-39)
Overall	12	24%	15 (9-46)	6 (0-41)	25 (11-55)

† Kaplan-Meier estimates of two year cumulative incidence
* in months (range)

Outcome

All patients survived and were followed for a mean time of 21.8 months (range 0.6-71.5). 12 (24%) children had neurological sequelae (table 1). Mild or moderate speech defects were detected in 9 children. One child with mild speech defects had additional motor impairments. Of three children with moderate speech defects two had also psychologic impairment and one also had motor impairments. All three severely affected children had psychomotor defects and developed epilepsy. The mean follow-up time of the affected children was 25 months (range 11 - 54) and of the unaffected children was 19 months (range 0.6-72). The sequelae appeared directly after the FSE in 5 patients and later on in 7 patients. All severe deficits were detected immediately after the FSE. The mean detection time of the mild deficits was 4 months and of the moderate deficits, 14 months.

Risk factors

The distribution of patient characteristics and their risks for neurological sequelae are shown in table 2. Two factors – longer seizures (HR 3.0) and the need for more than two different drugs needed for seizure termination (HR 5.2) – were correlated with the occurrence of sequelae in the univariate analysis. These factors were included in a multivariate proportional hazards model to examine their combined influence on the risk of sequelae. The number of drugs remained significant in the multivariate analysis (HR 4.2, CI 1.1-15.4), the duration was not significant (HR 1.9, CI 0.5-7.8).

Table 2 – Risks of sequelae in relation to patient and seizure characteristics

Characteristics	No. sequelae (N)	Sequelae (N)	Total (N)	Hazard ratio* (CI)
Gender				
male	28	9	37	1.6 (0.4-5.8)
female	17	3	20	rc
Age				
< 1	15	5	20	1.3 (0.4-4.0)
≥ 1	30	7	37	rc
Family history of seizures				
positive	6	2	8	1.2 (0.3-5.4)
negative	39	10	49	rc
Time of FSE				
day	20	4	24	rc
night	25	8	33	1.4 (0.4-4.6)
Temperature				
≥ 40°C	15	4	19	1.1 (0.3-3.5)
< 40°C	30	8	38	rc
Duration of FSE				
≤ 45 min	23	3	26	rc
> 45 min	22	9	31	3.0 (0.8-11.3)
Number of drugs				
≤ 2	36	5	41	rc
> 2	9	7	16	5.2 (1.5-18.1)

* Univariate hazard ratios with 95% CI compared with reference category (rc)

Discussion

The literature on the outcome of FSE in previously neurologically normal children contains conflicting results. A recently published population based study with 19 cases of FSE reported one child (5%) with sequelae and four children (21%) with further afebrile seizures .[3] Another population based study found epilepsy in 4% of the children with prolonged seizures by seven years of age .[13] No difference in full scale IQ between the children with FSE who developed no epilepsy and their sibling controls was found .[7] One clinic based study of 44 patients reported no neurological deficit nor further afebrile seizures .[1]

In the present clinic based study 5% of patients with FSE developed severe deficits, i.e. severely impaired speech development, psychomotor defects and epilepsy. Nineteen per cent developed mild to moderate sequelae, i.e. a six-month to two-year delay in speech development, with additional motor impairment in two

patients and psychologic disturbances in two patients. A speech deficit was present in all children with neurological sequelae (24%). The mean time between the episode of FSE and the detection of sequelae was 6 months.

Our study found a higher percentage of neurological sequelae than the three studies mentioned above.[1,3,13] Two of these studies were population based, and referral bias in the present study could partially explain the higher risk that was found .[14] Children in the Netherlands visit the public health service for general and developmental assessment at regular intervals.[15] Prior neurological deficits will be detected already .[16] FSE might have been the first presentation of epilepsy in the three patients with psychomotor sequelae and epilepsy. The children in Maytal's clinic-based study were followed mainly prospectively and none of them had neurological sequelae. The mean age at the occurrence of the FSE in that study was similar to our's and the follow-up time was even longer, but several children with previous febrile seizures were included.

No cause of the fever could be found in 51 % of the patients. Unknown viral infections might be possible in these cases, because viral serology was not routinely performed .[17]
Assessment of neurological development during follow-up in our study was performed by several doctors. This could have caused delay in the assessment and an underestimation of the risk of sequelae in our study. A hearing test was performed in only 50% of the children with speech delay; the parents of the other children reported no hearing defects. It is not likely that phenobarbital impaired speech development, because this agent has only a small negative influence on the child's cognitive functioning .[18]

Sex, age, temperature and family history were not risk factors of neurological sequelae in this study. Long duration of the seizure was found to be a risk factor in both the present study and in others.[1,4] This is in accordance with pathological studies that found a transitional period of 20 to 60 minutes from the start of the seizure. Thereafter, cerebral cell damage begins as a result of the increased metabolic rate and oxygen insufficiency .[19] The number of different drugs needed to terminate the seizure was the most important risk factor. If more than two different drugs were needed, a significantly higher probability of sequelae was observed.

Presumably both the number of drugs for seizure termination and the probability of sequelae are determined by the severity of the seizure. Therefore, we believe that the number of drugs is an indicator of the severity of the seizure. It was a better predictor of sequelae than seizure duration. This might be due to the fact that the medication for seizure termination was instantaneously recorded and accordingly the information is more accurate than information about the duration of the seizure. Thus our results are not in disagreement with the current view on the management of FSE. Rapid and vigorous treatment of the seizure is likely to stop further cerebral cell damage and to minimize development of sequelae.

We conclude that FSE may cause severe neurological sequelae in previously healthy children. The number of different drugs needed to terminate the seizure is significantly correlated with the risk of sequelae and may be used as an indicator of the severity of the seizure. The predominant developmental defect is speech deficit, which may appear after several months. We recommend monitoring FSE patients for at least one year so that language delay can be detected and intervention recommended as early as possible.

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PART III

PREVENTIVE USE OF ANTIPYRETIC DRUGS

Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures

6

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ABSTRACT

Objective *– To compare the antipyretic efficacy of ibuprofen syrup (5mg/kg per dose) and acetaminophen syrup (10mg/kg per dose) in children with a history of febrile seizures.*

Design *– Randomized, multiple-dose, double-blind, cross-over trial.*

Setting *– The outpatient department of a university affiliated teaching hospital.*

Patients *– Seventy outpatients (mean age, 2.1 years; range, 10 months to 4 years) who had visited the hospital because of a febrile seizure were randomized to treatment at a temperature of 38.5°C or higher.*

Interventions *– Study medication was given every 6 hours for 1 to 3 days. Rectal temperatures were recorded at 0, 2, 4, 6, 12 and 24 hours after the first dose.*

Main Outcome Measures *– The temperature 4 hours after the first dose, the mean temperature during treatment and the highest temperature during treatment were evaluated. Analysis of covariance corrected for the initial temperature, age, weight and cause of the fever.*

Results *– Ibuprofen lowered the initial temperature from 39.1°C to a mean temperature of 37.7°C during treatment; acetaminophen lowered the initial temperature from 39.2°C to 38.0°C. Ibuprofen reduced fever 0.50°C more than did acetaminophen at 4 hours (95% confidence interval [CI], -0.98 to -0.02). The mean temperature was 0.26°C lower during ibuprofen treatment (95% CI, -0.59 to 0.07); the highest temperature was 0.30°C lower (95% CI, -0.73 to 0.13). In 22 patients, a second fever was treated with the opposite medication than the first. In the crossover analysis, the respective differences were 0.66°C (95% CI, -1.29 to -0.06), 0.40°C (95% CI, -0.83 to 0.03) and 0.36°C (95% CI, -0.81 to 0.08) in favor of ibuprofen.*

Conclusions *– Ibuprofen and acetaminophen are effective antipyretic agents in children with a history of febrile seizures. Ibuprofen yielded significantly greater fever reduction than did acetaminophen 4 hours after the first dose. Research is needed on the value of antipyretic agents for the prevention of febrile seizure recurrence.*

Introduction

The incidence of fever as a symptom of infection in young children is high. Two percent to 5% of children experience a febrile seizure (FS); on average 30% of these have additional seizures.[1,2] The risk of recurrence may increase to 80% if risk factors are present.[3-5] Recurrent seizures increase medical costs and are upsetting for parents. Moreover, lengthy seizures may cause cerebral damage.[6] Therefore, it is worthwhile to try to lower the risk of recurrence of FS.

Because of the side effects of anti-epileptic medication in young children, the possibility of reducing the risk of additional seizures with ibuprofen or acetaminophen during fever is gaining interest.[7-9] Both medications are frequently used and their antipyretic efficacy has been proved.[10-12] They have a low incidence of side effects and are relatively safe[13-15], although acetaminophen overdoses may lead to irreversible hepatic necrosis.[16-18] To date, four double-blind clinical trials and one modified double-blind trial have compared the antipyretic efficacies of ibuprofen and acetaminophen in children.[10,11,19-21] These trials were in-hospital studies in which children with a history of FS were excluded; in only one study standard multiple doses were administered.[19] Therefore, we conducted a randomized, multiple dose, double-blind clinical trial to compare the antipyretic efficacies of ibuprofen and acetaminophen in outpatients with a history of FS.

Methods

Subjects

Patients who visited the Sophia Children's Hospital, Rotterdam, the Netherlands, because of an FS between June 1, 1991 and October 1, 1993 were eligible for participation in the study. FS were defined according to the National Institutes of Health, Bethesda, Md, consensus statement as a seizure associated with fever but without evidence of intracranial infection or a defined cause.[22] All eligible children were examined at special follow-up visits during which one investigator (AvE) obtained informed consent from the parents. Patients were enrolled in the study between June 1, 1992 and October 1, 1993 if they developed a

rectal temperature at home of 38.5°C or higher, were older than 10 months, and had no contraindication for ibuprofen or acetaminophen use. Patients were excluded if any antipyretic or antibiotic medication was taken within 12 hours before study entry.

A total of 141 patients with FS were eligible for participation; written informed consent was obtained from 117 (82%). One hundred and four fevers in 75 patients were reported and clinically evaluated, the other 42 patients never presented. Nine fevers in seven patients prompted prescription of antibiotics. Four of these patients were enrolled during a subsequent fever episode and three patients were never enrolled. Thus, 95 fevers in 72 patients were randomized to treatment. Three fevers in 2 patients showed major protocol violations and were excluded from the analysis (in two cases no measurements were performed; in the other case a mercury thermometer was used). Hence, a total of 70 children were evaluated; in 22 of these children, two episodes of fevers were included.

Procedures

The parents contacted the investigators at the occurrence of any feverish illness with a rectal temperature of 38.5°C or higher, as measured with a calibrated digital thermometer with a timer and a two-decimal temperature display (accuracy, < 0.16°C) that was provided by the hospital (Philips HP 5318, Eindhoven, the Netherlands). After the contact, the parents immediately visited the outpatient department (24-hour access). The attending investigator recorded the child's recent history and condition on a standard form. When all criteria for study entry were met, the parents gave their child the first medication dose while supervised by the investigator. They were provided with the study medication, a 10 ml oral syringe, and a form with the schedule of doses and temperature measurements. Rectal temperatures had to be recorded at 0, 2, 4, 6, 12, and 24 hours after the first dose was given. On the form the parents also recorded the actual time of each dose and measurement. The same procedures were followed at the occurrence of a second fever. The study was approved by the Medical Ethics Committee of the University Hospital Rotterdam.

Medications and randomization

Study medication was either ibuprofen syrup 20 mg/ml (5mg/kg per dose) or acetaminophen syrup 40 mg/ml (10mg/kg per dose), both administered every 6 hours. The medications looked and tasted identical and were provided in 100 ml bottles. The medication was given for one to three days, depending on the duration of the febrile illness. Subsequent fevers were included and treated according to a crossover design: if the first fever was treated with ibuprofen, the second was treated with acetaminophen, and vice versa. Balance between first-treatment assignments was achieved with the use of a computer generated random distribution in blocks of 6. Bottles were labelled with the respective patient and fever numbers in accordance with the randomization sequence. Patients and investigators were blinded as to the assigned medication.

Follow-up

One investigator (AvE) contacted the parents by telephone within 24 hours after administration of the first dose of medication. If required by the clinical condition of the child, a visit was made to the outpatient department for diagnostic re-evaluation and treatment. A scheduled follow up visit to the outpatient department took place within two to three days. The temperature list and the remaining medication were returned to the investigator. Every three months, free telephone interviews were conducted with the parents of all eligible children to increase participation.

Outcome and adverse events

Temperature measurements were evaluated if obtained at 2(+/-1), 4(+/-1), 6(+/-1), 12(+/-2) or 24(+/-2) hours after the first dose (note: parenthetical values are absolute). Outcomes in statistical analysis were the temperature at 4 hours after the first dose; the mean temperature of measurements, if available, at 2, 4, 6, 12, and 24 hours; and the highest temperature of the respective measurements. We studied the temperature at 4 hours after the first dose because previous studies demonstrated maximal fever reduction at 4 hours.11 19 The mean temperature of measurements at 2, 4, 6, 12, and 24 hours was used as an overall measure, and the

highest temperature of the respective measurements was studied because it is assumed that FS will occur above a certain temperature threshold.[23] Adverse events were defined as new (or changes in) clinically important symptoms, sensitivity reactions or injuries during the study, whether or not related to the treatment.

Statistics

Normality of the outcome values was tested using normal plots and the Shapiro-Wilk W test.[24] In a parallel group analysis the patient's first fevers were evaluated. Differences between the treatment groups in the performance of the respective measurements were analyzed with Pearson's Chi square test. Temperature differences between patients treated with ibuprofen and acetaminophen were analyzed by two sample t-tests and analysis of covariance.[25] Missing data were handled by taking the mean of available (not missing) values. Potential confounders were the initial temperature, cause of fever, age, and weight. Cause of fever was divided into three subgroups: one focus of upper respiratory tract infection (simple URTI), more foci of URTI (extended URTI), and other infections. The potential confounders were used in the analysis of covariance if their univariate association with the outcome had a P value lower than 0.20. A crossover analysis comparing ibuprofen and acetaminophen within the same patient was performed for verification of the results of the first fever analysis. The difference between the patient's initial temperatures was used as covariate. Potential confounders were compared between patients with two fevers and patients with only one fever to check for selection of crossover patients (t-test). The two sample t-test was used to check for treatment-period interaction (i.e. carryover of treatment effect from one period to the next), and the paired t-test was used to check for period effects.[26]

Results

Table 1 (overleaf) shows the initial characteristics of the 70 patients enrolled in the study, according to the assigned treatment during the first episode of fever. The initial temperature was 0.11°C higher in the acetaminophen group. Upper respiratory tract infections were the most common cause of fever, in 17 patients no focus of infection was found. Extended URTIs were more common

Table 1 – Baseline characteristics at inclusion of the first fever*

Characteristic	Ibuprofen (N=34)	Acetaminophen (N=36)
Male, %	71%	53%
Age, mo	25.0 (10.8)	24.7 (9.5)
Weight, kg	13.2 (2.8)	12.6 (2.2)
Initial temperature, °C	39.12 (0.83)	39.23 (0.79)
Cause of fever, %†		
simple URTI	44	33
extended URTI	24	42
other	32	25

* Values are mean (SD) unless otherwise indicated
† Simple upper respiratory tract infection (URTI) indicates one focus; extended URTI, more than one focus; and other, other infections

in the acetaminophen group. Other characteristics were present with similar frequency in the two treatment groups. Twenty-four

children (34%) entered the study immediately after an FS, equally distributed among the treatment groups (12 in each group).

Compliance and withdrawal

Patients were included at a median of 2.3 hours after fever was noticed. In six episodes of fever, the parents discontinued the treatment within 24 hours because of complete recovery (3 ibuprofen, 3 acetaminophen). Ninety-seven percent of the scheduled doses were given in both treatment groups. The parents moved the 12-hours dosage forward two hours in one patient in the acetaminophen group, the 18-hours dosage was moved forward two hours in 4 patients (two in the acetaminophen group and two in the ibuprofen group) and the 24-hours dosage was moved forward four hours in one patient in the acetaminophen group. Overall, 91% of scheduled measurements were performed. The parents performed all scheduled measurement in 62% (21) of ibuprofen treated children and in 69% (25) of acetaminophen treated children.

First fevers

Table 2 summarizes the results of the first episodes of fevers. The proportion of performed measurements was highest at 6 hours and 12 hours in both groups. More 24-hour measurements were per-

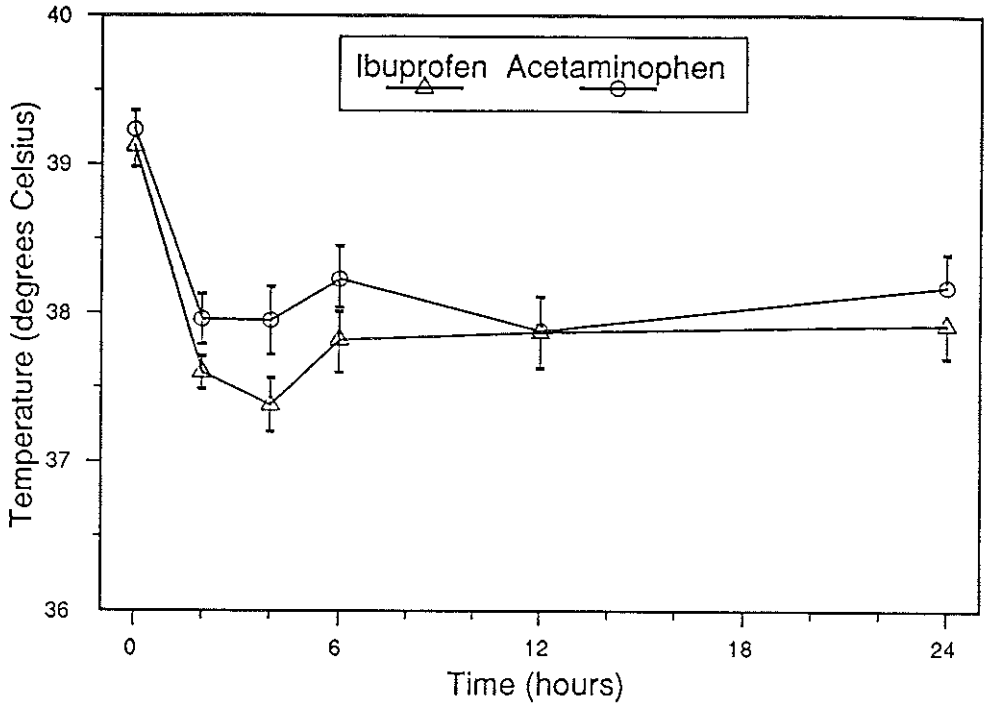
Table 2 – First fevers: number of recordings, mean (SEM) temperatures, and number of recordings below 38.5°C, by treatment allocation

Time after first dose, h	No. (%)	Mean (SEM) temperature, °C	No. (%) <38.5°C
Ibuprofen			
0	34 (100)	39.12 (0.14)	8 (24)
2	30 (88)	37.60 (0.11)	27 (90)
4	31 (91)	37.38 (0.18)	26 (84)
6	34 (100)	37.82 (0.22)	20 (59)
12	32 (94)	37.87 (0.24)	21 (66)
24	27 (79)	37.92 (0.22)	20 (74)
Acetaminophen			
0	36 (100)	39.23 (0.13)	4 (11)
2	29 (81)	37.96 (0.17)	22 (76)
4	31 (86)	37.95 (0.23)	22 (71)
6	35 (97)	38.23 (0.22)	18 (51)
12	35 (97)	37.88 (0.19)	24 (69)
24	33 (92)	38.18 (0.22)	20 (61)

formed in the acetaminophen group (92%) than in the ibuprofen group (79%, p=0.14). Omission of 24-hour measurements was mostly owing to recovery of the child. The initial temperature at the emergency department of 8 children receiving ibuprofen and of 4 children receiving acetaminophen was lower than 38.5°C, although temperatures at home had been 38.5°C or higher. During acetaminophen treatment, the temperatures were higher, and fewer children had temperatures below 38.5°C. Ibuprofen lowered the initial temperature from 39.1°C to an average temperature during treatment of 37.7°C, acetaminophen lowered the temperature from 39.2°C to 38.0°C. The mean temperatures stayed low for 24 hours during both treatments (figure, overleaf). The temperature at 4 hours in the ibuprofen group was 0.6°C lower than that in the acetaminophen group and the mean and highest temperature during treatment were 0.3°C lower (table 3, overleaf). After adjustment for the covariates similar results were found and there was a significant difference of 0.50°C at 4 hours in favor of ibuprofen.

Fevers within the same child: crossover analysis

In 22 children a second episode of fever was included. The mean time between the two fever episodes was 2.1 months (range 0.2-7.7). No significant difference was found between the 22 crossover patients and the 48 patients with one fever. Furthermore, neither a



Mean temperatures over time for first fevers treated with ibuprofen and acetaminophen. Bars indicate SEMs.

Table 3 – Results of first fevers analysis: differences in temperature between fevers treated with ibuprofen and those treated with acetaminophen*

End point by method	Covariate	T difference (95% CI)	*P*
T4			
t test		-0.57 (-1.15 to 0.01)	.05
Analysis of covariance	T0, diagnosis, age	-0.50 (-0.98 to -0.02)	.04
Tmean			
t test		-0.28 (-0.68 to 0.13)	.17
Analysis of covariance	T0, diagnosis	-0.26 (-0.59 to 0.07)	.13
Tmax			
t test		-0.31 (-0.80 to 0.17)	.20
Analysis of covariance	T0, diagnosis	-0.30 (-0.73 to 0.13)	.18

* T difference indicates ibuprofen-treated fevers minus acetaminophen-treated fevers (n=70, 70 periods); T4 temperature at 4 hours after first dose; Tmean, average of temperatures at 2, 4, 6, 12, and 24 hours after first dose; Tmax, highest temperatures at 2, 4, 6, 12, and 24 hours after first dose;TO, initial temperature; and diagnosis, cause of fever (simple upper resipratory tract infection, extended upper respiratory tract infection, or other infection).

significant time effect nor a significant carry over effect was found. Ibuprofen reduced temperature at 2, 4, 6, and 12 hours more than acetaminophen (table 4). Furthermore, temperatures were more often below 38.5°C during ibuprofen treatment. The differences in temperature reduction were greater than in the first fever analysis (table 5). The corrected differences were similar to the crude differences; the difference at four hours (0.66°C) remained significant.

Adverse events and seizures

Fourteen adverse events were recorded in nine patients. Six events occurred during ibuprofen treatment and eight occurred during acetaminophen treatment. Five FS occurred during treatment – two with ibuprofen and three with acetaminophen. The other adverse events were gastro-intestinal complaints (two with aceta-

Table 4 – Crossover analysis: number of paired recordings, mean (SEM) difference of temperatures, and difference between number of recordings below 38.5°C in the same child

	Ibuprofen minus acetaminophen					
Measurement	0 h	2 h	4 h	6 h	12 h	24 h
Paired no. (%)	22 (100)	17 (77)	16 (73)	19 (86)	19 (86)	17 (77)
Mean (SEM) temperature difference	0.04°C (0.16°C)	-0.33°C (0.17°C)	-0.67°C (0.29°C)	-0.65°C (0.36°C)	-0.41°C (0.44°C)	0.04°C (0.32°C)
Difference between no. <38.5°C, no (%)	1(5)	6 (35)	5 (31)	4 (21)	3 (16)	2 (12)

Table 5 – Results of crossover analysis: differences in temperature between ibuprofen-treated fevers and acetaminophen-treated fevers in the same child*

End point by method	Covariate	T difference (95% CI)	*P*
T4			
t test		-0.67 (-1.29 to -0.06)	.03
Analysis of covariance	T0	-0.66 (-1.15 to -0.16)	.02
Tmean			
t test		-0.39 (-0.85 to 0.08)	.10
Analysis of covariance	T0	-0.40 (-0.83 to 0.03)	.09
Tmax			
t test		-0.36 (-0.82 to 0.10)	.12
Analysis of covariance	T0	-0.36 (-0.81 to 0.08)	.13

* T difference indicates difference between ibuprofen-treated fevers and acetaminophen-treated fevers (crossover analysis: n=22, 44 fevers). See footnote in table 3 for expansions of additional abbreviations.

minophen treatment), exanthemas (one with ibuprofen and two with acetaminophen treatment), insomnia (one with ibuprofen treatment) and hypothermia (temperatures 35°C to 36°C; two with ibuprofen and one with acetaminophen treatment).

Discussion

In our study, ibuprofen and acetaminophen (Paracetamol) suspensions were shown to be effective antipyretics in children with a history of FS. Ibuprofen treatment (5mg/kg/dose) resulted in lower temperatures than acetaminophen treatment (10mg/kg/ dose). Four hours after the first dose the difference was statistically significant. A crossover analysis confirmed the results of the first fever analysis.

Because the antipyretic action of ibuprofen and acetaminophen was sufficiently demonstrated in several double-blind placebo controlled studies, a placebo control group was considered redundant for this trial.[10,11,20] Moreover, ibuprofen 5mg/kg/dose and acetaminophen 10mg/kg/dose were demonstrated to yield equal temperature reduction and a small incidence of side effects in a previous study.[10] Accordingly, we chose to compare these low therapeutic doses in children with previous FS. The time of maximal fever reduction was determined at four hours after the initial dose in two other studies.[11,19]
We therefore selected the temperature at four hours as one of the end points for statistical evaluation. The mean temperature during treatment was considered as the most suitable end point to compare the overall antipyretic effects. We also introduced the highest temperature during treatment as an endpoint, because it is assumed that FS will occur above a certain temperature threshold.[23] Because initial temperature and age interacted with the temperature during treatment in two previous studies, analysis of covariance was used to correct for these variables and for the potential confounders weight and cause of fever.[11,27]

In this outpatient study measurements in all patients were performed with one type of thermometer. The parents received instruction immediately before the beginning of each treatment period. Compliance with the schedule of dosing and measuring was high. We therefore believe our findings to be reliable.

Both treatments lowered the temperature to a minimum at four hours, and the mean temperature remained low. Comparison of the 4-hour measurements showed a significantly lower temperature with ibuprofen treatment. In a previous study[10] that compared ibuprofen 5mg/kg/dose and acetaminophen 10mg/kg/dose, temperatures at four hours were 0.4°C lower with ibuprofen than with acetaminophen. Two other studies[20,21] used higher doses of ibuprofen (7 and 7.5mg/kg/dose) and found significantly lower temperatures between three and five hours after the initial dose of ibuprofen. Higher doses of acetaminophen (12 and 15mg/kg/dose) were used in two other studies, but little or no difference compared with ibuprofen 5mg/kg/dose was detected at the time of maximal fever reduction.[11,19] We found that the difference of the mean temperatures during treatment was smaller than the difference at four hours. This can partially be explained by the smaller proportion of 24-hour measurements performed in ibuprofen-treated children. Omission of 24-hour measurements was mainly seen in children who had made a complete recovery, thus decreasing the difference of the mean temperatures between the treatments. In two other studies the difference of the mean temperatures also became smaller after the first six hours.[19,21] In one other study ibuprofen 7mg/kg/dose showed a significantly lower mean temperature during treatment than acetaminophen.[21]

Although only 22 children received the second period treatment, the results of the first fever analysis were confirmed in the crossover analysis. In this analysis, which eliminates interpatient variability, fewer patients are necessary for detection of a treatment difference.[28] As in the first fever analysis, temperatures at all endpoints were lower during ibuprofen treatment. The differences between the two treatments were even greater than in the first fever analysis, and the difference at four hours remained statistically significant.
A treatment-period interaction was very unlikely because both drugs have a half-life of two hours and the shortest interval between two treated fevers was two weeks.[29]

To our knowledge, ours is the first study that compares the antipyretic efficacies of ibuprofen and acetaminophen in children with a history of FS. Our results are similar to those of Walson et al.[10],

who compared the same doses in children without FS. Our results are also in agreement with those of studies that used higher doses of ibuprofen or acetaminophen. From this we, conclude that the antipyretic efficacy of ibuprofen and acetaminophen is similar in children with and children without a history of FS.

Clinicians may pursue rapid fever reduction in children who have shown to be susceptible for FS. In this respect, we think 0.5°C greater temperature reduction at four hours with ibuprofen to be a clinically relevant finding. Ibuprofen might therefore be the best candidate for treatment to prevent FS. Few recurrent seizures occurred in this study, and seizure prophylaxis could not be evaluated as the expected number of recurrences was too small and no placebo groups were used. A larger placebo controlled trial is necessary to determine whether antipyretic agents can prevent febrile seizure recurrences.

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Potential efficacy of antipyretics in the prevention of febrile seizure recurrence

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ABSTRACT

To estimate the potential preventive effect of antipyretics on recurrence of febrile seizures (FS) we compared the recurrence risk in 109 children who were offered treatment with ibuprofen or acetaminophen syrup during fever with the recurrence risk in 103 children who were not offered antipyretic treatment. Children had had an FS between one and three years of age and were seen at the outpatient department of the Sophia Children's Hospital, Rotterdam. Recurrences were prospectively recorded in both study groups. In an intention-to-treat analysis, the number of recurrences per fever and the risk of any recurrence were compared. An on-treatment analysis compared the number of recurrences per fever between the control group and compliers who actually received medication in the treatment group. Effect measures were odds ratio (OR) as estimated by the Mantel-Haenszel procedure and hazard ratios (HR) as estimated by Cox regression.

According to the intention-to-treat analysis the recurrence risk per fever was 15% in the treatment group and 12% in the control group (OR 1.2; 95% CI 0.7-2.3). The hazard ratio of any recurrence in the treatment group compared to the control group was 1.1 (95% CI 0.7-1.8). In the on-treatment analysis, the recurrence risk in the treatment group was estimated much lower than in the control group (6.9% versus 12%, OR 0.5, 95% CI 0.2-1.3).

We conclude that 50 percent reduction of FS recurrences may be acquired by adequate use of antipyretic syrup during fever. Accordingly, one would need to treat adequately around 20 fevers in children with a previous FS to prevent one seizure recurrence. This hypothesis needs to be confirmed in a randomized clinical trial.

Introduction

Febrile seizures (FS) are the most common type of seizure in children. In three to five percent of children at least one FS occurs before the age of six years.[1,2] FS is described as a sudden loss of consciousness with or without myoclonic jerking during fever; intracerebral or metabolic causes are excluded. A typical FS lasts for 5 to 10 minutes. FS frequently recur at a new febrile episode: the overall risk of one or more recurrences is about 30%.[2-4]

The risk of recurrence is increased when there is a first degree family history of seizures, a temperature below 40°C at the initial seizure or a history of previous recurrences.[5] Half of the recurrences occur within six months of the first seizure, three quarters within a year, and 90 percent within two years.[6,7,8] Though the prognosis of children with seizures lasting less than 30 minutes is good, recurrent seizures are upsetting for both parents and children and recurrent seizures increase medical costs. Moreover, seizures lasting longer than 30 minutes may cause cerebral damage.[9] Thus, it is worthwhile to try to lower the risk of recurrence of febrile seizures.

Recurrent febrile seizures may be prevented by means of continuous treatment with anticonvulsive drugs or intermittent treatment (during fever) with diazepam. These drugs, however, have a high incidence of unfavorable side effects, notably on behavior and intellectual development.[10,11] Recently, the possibility of intermittent seizure prophylaxis with antipyretics has gained interest. Antipyretics have a low incidence of side effects and are relatively safe.[12,13] They are frequently used in children and their antipyretic efficacy is well established.[14] However, no randomized clinical trial has been done so far.
We performed a comparison on the currently best available data to estimate the prevention of FS recurrences that may be expected in a randomized clinical trial (RCT) and to estimate the required sample size for such a trial. We also calculated the number of fevers to be treated to prevent one recurrence. Therefore, we compared the FS recurrence risk in children between a treatment group of children participating in a clinical trial of ibuprofen and acetaminophen syrup during fever[15], and a control group of children who were not routinely given antipyretics during fever.[6]

Methods

Patients and procedures

Patients
Children who visited the Sophia Children's Hospital because of a febrile seizure (FS) experienced between the age of 10 and 36 months were studied. FS was defined in accordance with the NIH consensus statement of 1981, as a seizure associated with fever

but without evidence of intracranial infection or a defined cause.[16] Children were identified by use of the hospital record registration system and the logbook of outpatient visits. The children's histories were completed during special outpatient follow-up visits. Date of the seizure, seizure characteristics, rectal temperature and first degree family history of seizures were recorded on standardized forms. Children with neurological diseases (e.g. epilepsy, psychomotor retardation) and children receiving continuous treatment with anti-convulsive drugs were excluded.

Treatment group

The treatment group consisted of 109 children with one or more previous seizures who visited the Sophia Children's Hospital between June 1, 1991 and October 1, 1993, and who were included in a randomized double blind trial of ibuprofen and acetaminophen during fever.[15] This trial aimed to compare the antipyretic efficacy of ibuprofen and acetaminophen in FS children. Written informed consent was obtained from the parents of 114 children; from 109 patients data on recurrences could be obtained; 5 children were lost to follow-up. The parents of 72 children complied with the treatment protocol at the occurrence of a subsequent fever and visited the outpatient clinic to receive the study medication for one or more days. The other 37 children had not visited the outpatient clinic. The 72 children who actually visited the hospital used the study medication for one or two days. 22 patients visited the hospital more than once for a febrile period. Seven patients also received antibiotic treatment.

Control group

The control group consisted of 103 children with a first FS who visited the Sophia Children's Hospital between February 1, 1988 and February 1, 1990. The children participated in a follow-up study on FS recurrences (n=115).[6] The parents had given consent for participation on the first follow-up visit. Twelve children had had their first FS above three years of age and were excluded, leaving 103 for the present analysis. The treating physicians advised the parents not to use any antipyretics.

Follow up and measurements

Both the treatment and the control group were studied by the same investigators in the same setting as part of an ongoing follow-up study. Base line characteristics of all children were

recorded on standardized forms. All children were prospectively followed for FS recurrences from the date of their first FS or from the date of informed consent (e.g. first FS or a FS recurrence).
In the treatment group, compliance was enhanced by a three monthly telephone interview with the parents. According to the treatment protocol, a visit to the hospital was made when a rectal temperature ≥38.5°C was measured at home. The mean follow up period in this group was 0.6 year.
The control group was seen on a scheduled follow-up visit one to three months after the initial seizure. Hospital visits at subsequent fevers were only made if required by the medical condition of the child. The parents were asked to report recurrences to the investigator and to record fevers. At two years after the initial FS, the parents were contacted by the investigator to complete ascertainment of fevers and seizures, if necessary.

Statistical analysis

The incidence of the outcome 'febrile seizure recurrence' was either calculated as the risk of a recurrence per fever (number of recurrences divided by number of fevers) or as the cumulative incidence of any recurrences at 3 years of age. In an intention-to-treat analysis both outcomes were evaluated, in an on-treatment analysis only the first outcome was used.

Intention-to-treat analysis
In this analysis all children of whom the parents gave written informed consent were included (table 1). The number of recurrences per fever was calculated in the treatment-group and in the control-group. In the treatment group only fevers and recurrences within the study period were taken into account. In 14 children the number of fevers was unknown; they were excluded from the analysis, leaving 95 children.
In the control group one child with an improbable number of fevers was excluded from the analysis, leaving 102 children. The number of recurrences per fever and crude and adjusted risk ratios, which may be interpreted as relative risks, were calculated. Odds ratios were adjusted for first degree family history of seizures and temperature at the initial seizure by stratification with the Mantel-Haenszel procedure.[17]

Table 1 – Overview of analyses and methods used

Analysis	Outcome	Study group	Start at risk	Effect	Covariates
Intention-to-treat	Recurrences per fever	Treatment	Inclusion in trial	Recurrence risk Odds ratio	Fhx†, T40‡
		Control	Initial FS*		
	Any recurrence	Treatment	Age at inclusion in trial	Cumulative risk Hazard ratio	Fhx†, T40‡, rec1§, rec2§, 6 months¶
		Control	Age at initial FS*		
On treatment	Recurrences per fever	Treatment	Inclusion in trial	Recurrence risk Odds ratio	Fhx†, T40‡
		Control	Initial FS*		

* Febrile seizure
† Positive first degree family history of FS
‡ Temperature <40°C at initial seizure
§ One/two recurrences in history
¶ Seizure within last six months

Furthermore, cumulative risks of any FS recurrence at 3 years of age were estimated with Kaplan-Meier survival analysis.[18,19] All children were included in this analysis. Left censoring was used for the entry time of children in the treatment group, which was specified as the age at the date of informed consent. The entry time of the children in the control group was set at the age of their first FS. Multivariate Cox proportional hazard regression models were used to adjust for the effect of the risk factors family history, temperature at the first seizure, and the presence of previous recurrences on the probability of subsequent febrile seizures.[20] Hazard ratios (HR) with 95 percent confidence intervals (CI) were computed to compare risks between treatment and control children. The hazard ratio is interpreted as a relative risk. The EGRET statistical package was used for computation.

On-treatment analysis

In this analysis the number of recurrences per fever was evaluated (table 1). The treatment group was restricted to fevers of children who had actually visited the hospital and received the study medication. Seventy-two children who received treatment according to the protocol were considered for the on-treatment analysis. Six children of whom the parents contacted the investigator after the child's recurrence were excluded from analysis. These recurrences had occurred at home after a febrile period of 1.5 to 14 hours. Thus, the remaining number of analyzed children was 66 in the

Table 2 – Clinical characteristics of patients

Feature	Treatment (n=109) n(%)		Control (n=103) n(%)	
Age at entry (first FS* or inclusion in trial				
< 1 y	15	(13%)	27	(26%)
1 – 2.5 y	78	(71%)	72	(70%)
> 2.5 y	16	(15%)	4	(4%)
Male	68	(62%)	65	(63%)
Seizures in first degree relative	12	(11%)	21	(20%)
Initial seizure characteristics				
Mean age (years)	1.5		1.4	
Temperature <40°C	37	(44%)	62	(62%)
Number of seizures before entry				
1	93	(85%)	103	(100%)
2	12	(11%)	0	–
≥ 3	4	(4%)	0	–
Mean follow-up (years)	0.6		2.2	

* Febrile seizure

treatment group, who had experienced 79 fevers. Twelve children who were randomized to treatment after a seizure but who experienced no further fevers during follow-up did not contribute to the analysis.
The control group (n=102) consisted of the same children as was used for the computation of the number of recurrences per fever in the intention-to-treat analysis. Analogously, the analysis is described in the former section.

Results

Intention-to-treat analysis

Table 2 shows the characteristics of the children who were included in this analysis. More children with age under 1 year at the initial FS were present in the control group. The distribution of gender was similar in the control and treatment group. More children in the control group had a positive family history or temperature under 40 degrees Celsius at the initial seizure. The mean

Table 3 – Numbers of children, recurrences, fevers, and recurrence risks

Analysis	Outcome	Study group	No. of children	No. of recs*	No. of fevers	Effect		
						Risk	RR†	95% CI‡
Intention-to-treat	Recs* per fever	Treatment	95	17	115	15%	1.3	CI=0.7-2.4
		Control	102	59	482	12%	rc§	–
	Any recs*	Treatment	109	21	–	56%¶	1.1	CI=0.7-1.8
		Control	103	64	–	58%¶	rc§	–
On-treatment	Recs* per fever	Treatment	66	5	79	6.8%	0.5	CI=0.2-1.3
		Control	102	59	482	12%	rc§	

* Recurrences
† Adjusted relative risks
‡ 95% confidence interval
§ Reference category
¶ Cumulative recurrence risk at 3 years of age

follow-up of the control group was longer than that of the treatment group: 2.2 versus 0.6 years.

Table 3 summarizes the results of the analysis. 95 children in the treatment group were analyzed and had a 15% recurrence risk per fever. In the control group 102 children had a recurrence risk of 12%. The crude risk ratio was 1.2 (95% CI: 0.7-2.2). The adjusted risk ratio was 1.3 (95% CI: 0.7-2.3).
The risk of any recurrence did not substantially differ between the treatment group and the control group (table 3). The univariate hazard ratio for any recurrence was 1.0 (CI 0.6-1.6), the adjusted hazard ratio was 1.1 (CI 0.7-1.8).

On-treatment analysis

The distribution of the base-line characteristics of the treatment (n=66) and the control group (n=102) in the on-treatment analysis were similar to the distribution shown in table 2. More children of age > 2.5 years were present in the treatment group. More children in the control group had a positive family history or temperature under 40 degrees Celsius at the initial seizure. Distribution of gender and temperature at the first seizure were comparable between the study groups. The median follow-up in the treatment group was 1.5 years shorter than in the control group.

Seventy-nine fevers were included in the treatment group. Table 3 shows that five recurrences occurred in the treatment group, resulting in a 6.8% (5/79) recurrence risk. In the control group the recurrence risk was 12% (59/482). Thus, a 5.4% lower recurrence risk was acquired in the treatment group (p=0.10). This means that around 20 fevers would have to be treated to prevent one recurrence. The crude risk ratio for seizure recurrence in the treatment group was 0.5 (CI 0.2-1.2) and the adjusted risk ratio was 0.5 (CI 0.2-1.2; table 3).

Discussion

During the past ten years continuous prophylaxis with antiepileptic drugs such as phenobarbital and valproate has become less frequently used to prevents FS recurrences, because of it adversely influences the child's development.[10,21,22] Recently, a modest effect (33% reduction in two-year risk of recurrence) of intermittent treatment (i.e. during fever) with oral diazepam in the prevention of seizure recurrences was demonstrated.[11] Yet, only 50% of the parents of eligible children were willing to cooperate with that treatment protocol. Ataxia, lethargy, irritability and other side effects occurred in 39% of the children treated with diazepam. Therefore, in our opinion the advantages of this treatment (decrease of recurrence risk of febrile seizures) do not countervail the disadvantages (i.e. high incidence of side-effects).[23]

Intermittent prophylaxis of FS recurrences with effective doses of antipyretic medication may be well feasible. One large study showed that only four percent of the recurrences occurred before fever was noticed, which supports that medication can be given on time.[24] Two recent studies showed little or no effect of intermittent prophylaxis with antipyretics, but the methodology can be questioned: firstly, a comparison between acetaminophen given every four hours and acetaminophen given above 37.9°C only showed no difference in incidence of further seizures within 24 hours.[25] These seizures were defined as early 'recurrences'. However, such recurrent seizures are generally considered as multiple or complex, and are not considered as subsequent recurrences. Secondly, a recently published placebo controlled study showed no unequivocal preventive effect of acetaminophen, nor of acetaminophen in combination with diazepam.[26] However, additional doses of acetaminophen

were recommended in all children if the temperature rose above 39.5°C while using study medication. This may very well have prevented recurrences in this study, since in more than 50 percent of the children seizures only occur when the temperature exceeds 40°C.[8]

So far, a treatment policy of routine administration of antipyretics during fever has not been compared with a no-treatment policy. We performed a comparison on our currently available data to estimate a minimal and maximal prevention of recurrences that may be expected. We tried to simulate a randomized clinical trial (RCT), using a treatment group of children who participated in a trial with ibuprofen and acetaminophen and a recent prospective follow-up study as a historical control group. No reduction of recurrences was found in the intention-to-treat analysis, while we observed a nearly 50 percent reduction of seizure recurrence risk per fever in the on-treatment analysis.

Because the present study did not include randomization between the two treatment arms, comparability of the prognosis between the study groups was not guaranteed. Important similarities of both study groups were the same clinical setting, the same reference population, the same investigators who used the same definition of febrile seizures.[27] The somewhat dissimilar distribution of family history of seizures and the temperature at the initial seizure between treatment and control group could be statistically corrected for in both intention-to-treat and on-treatment analysis. The FS recurrence risk of FS decreases with age; younger age at entry and shorter follow-up time in the treatment group therefore may have caused an upwardly biassed risk ratio (OR 1.3). Survival analysis could not be performed in the on-treatment analysis, because of discontinuity of time due to the exclusion of recurrences. In the intention-to-treat analysis however, Kaplan-Meier and Cox survival analysis by their nature corrected for differences in follow-up time between the treatment group and the control group. When these analyses also corrected for age at entry and the number of previous recurrences; a hazard ratio near unity (HR 1.1) was obtained. Retrospective registration of the number of fevers in the control group was another possible limitation of comparability with the treatment group. Recurrences were recorded prospectively in both groups and are probably better recalled than fevers. The risk of a

recurrence per fever in the control group may therefore be biased in either direction.

We believe the results of the intention-to-treat analysis to be a conservative estimate of the treatment effect. Compliers with the treatment protocol were included together with non-compliers, who stayed at home or visited the emergency department only after a recurrence.
The on-treatment analysis takes only into account who came directly to the hospital for treatment and provides a much more optimistic estimation. This suggests that FS recurrences could be prevented if antipyretic medication would be readily available. The recurrence risk per fever in our study decreased 5 percent (from 12 to 7%). If we assume these figures to be actual, around 20 fevers would have to be treated to prevent one recurrence. This seems a small effect for the generally benign disease as FS is. However, a halving of the recurrence risk might be worthwhile to warrant the execution of a randomized trial in children with a high recurrence risk. This high risk group might be defined as children with one or more of the following characteristics: age < 1 year, previous recurrences, temperature < 40°C at the first febrile seizure.[5] To test the hypothesis that treatment would decrease recurrence risk from 50% to 25%, a sample size of 230 children is needed for a RCT. We are currently performing a double blind randomized controlled trial comparing the efficacy of ibuprofen versus placebo for prevention of recurrent seizures in children with a high recurrence risk.

In conclusion, we observed a nearly 50 percent reduction of seizure recurrence risk per fever in the on-treatment analysis. No reduction of recurrences was found in the intention-to-treat analysis. There are several limitations of the present design that may have accounted for this lack of effect. We have to consider dilution of the treatment effect likely in the intention-to-treat analysis. Furthermore, the results of the on-treatment analysis should be viewed in the light of its experimental setting. In practice, these results may not be achieved because fever may not be noticed before seizure occurrence and antipyretics may not always be immediately available. Therefore, we expect the magnitude of the real preventive effect to lay between the results of these two analyses. This research supports the need of a double blind randomized controlled trial of antipyretics versus placebo for prevention of recurrent febrile seizures.

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PART IV

GENERAL DISCUSSION

8 General discussion

General aspects

Fever

Fever is defined as a temperature above normal. Considerable differences between children exist regarding their normal body temperature. The temperature of the individual healthy child may vary over the day from 36°C to 38°C, depending on the time of the day, sleep, feeding and activity.[1] Also, an increase of the temperature to 38.5°C may be caused by physical exercise, warm clothing, and hot or humid weather.[2] There is little agreement about the temperature at which normal temperature stops and fever starts. Different authors use different temperatures to define fever in children: 38.0, 38.5 or even 38.8°C are used.[2-6]
The measured body temperature also differs with the method of assessment: rectal, oral or axillary temperatures.[3] When performed in a standardized way, rectally measured temperature gives the best approximation of the actual body core temperature.[7,8] To date, most studies use electronic thermometers with digital display and beep signal, which is less prone to reading errors and makes standardized measurements possible.
Because a febrile seizure (FS) is defined as a seizure during fever, the temperature at the time of a febrile seizure is important. It will result in the diagnosis of FS or of some form of epilepsy.[9] In accordance with other authors, we defined fever as rectally measured body temperatures of 38,5°C or more.[10-11] In the present studies a seizure was considered a FS when rectal temperatures of 38.5°C or more were measured between two hours before until two hours after seizure occurrence.

Febrile seizures and febrile status epilepticus

Febrile seizures (FS) were described in accordance to the National Institute of Health (NIH) Consensus Meeting of 1981 as '...an event in childhood, usually occurring between three months and five years of age, associated with fever but without evidence of intracranial infection or defined cause'.[9] A seizure is defined as '...an episode of alteration in motor, sensory or behavioral function, with or without loss of consciousness...'.[12] Most FS, either generalized with tonic and clonic components or focal, result in loss of consciousness which lasts not more than 10-15 minutes, after which the majority of patients spontaneously recover. The actual attack is therefore mostly not witnessed by the physician, who has to rely on the clinical history to make sure that a seizure has occurred to make the diagnosis of an FS and to assess its duration. This is a major challenge for the clinician, since several conditions may mimic a seizure. The differential diagnosis of an FS is discussed in the introduction chapter. The duration is more difficult to assess; it has to be inferred from the history taken from the parents and the doctor's observations in the emergency room. Most parents are not able to take good notice of the duration of their child's seizure, because of the acuteness and emergency of the situation.
Some earlier studies defined febrile status epilepticus (FSE) as a seizure lasting > 60 minutes.[13] Most recent studies use a minimum duration of 30 minutes.[14,15]
To date, there is general agreement between clinicians on the classification of a seizure whether the seizure is prolonged or not, and the inter-rater agreement is good.[16-18] In the present study, a FSE is defined as either one seizure lasting more than 30 minutes or as a series of seizures of the same total duration without definite recovery in the interictal phases.[19,20]

Study population

The population of FS children in follow-up consists of children who visited the outpatient department of the Sophia Children's Hospital in Rotterdam due to an FS. This is an university hospital in the inner city of Rotterdam, with a general paediatric outpatient department. About 2,300 new patients a year visit the emergency unit of the outpatient department.[21] FS accounts for 3.6% (n=80) of all new patient visits. The outpatient clinic has a direct access: 25% of outpatient visits are without referral.[22] Our study popula-

tion consists of approximately 70% children with simple febrile seizures.[11] In a recently published pooled analyses of FS children from five international studies, a previous follow-up study from our clinic was included. No major differences in prevalence of risk factors existed between the three clinic-based and two population-based studies, although the prevalence of lengthy FS was higher in the Dutch study. Two studies found that general practitioners in the Netherlands refer respectively 30% and 45% of patients with a first FS to the hospital.[23,24] Vink et al. found that most general practitioners in Rotterdam refer children who had seizures with duration over 15 minutes or other complex features.[24] In our study of FSE, most patients with lengthy febrile seizures (FSE) were referred by either the general practitioner or pediatrician of other hospitals. The study patients were selected from clinical and outpatients with FS, recorded as a first FS and with a seizure duration of more than 30 minutes.
Thus, the overall selection effect in our FS studies is probably not very great; a considerable selection effect is likely to be present in the study of FSE.

Since 1988, we follow children who visited the Sophia Children's Hospital in Rotterdam with an FS. According to the follow-up program, standard follow-up visits to one of the investigators is arranged. During the visit, the investigator performs a physical examination of the child and has an interview with the parents.
The distribution of different ethnic groups in our study population (40% non-West European) reflects the diversity in representation of the city of Rotterdam.[22]

Febrile seizures, febrile status epilepticus and outcome

Typical FS are benign and no short-term sequelae are found.[25] The long-term prognosis is also favorable. No difference in IQ at 7 years of age between FS children and their siblings is found.[26] The risk of epilepsy after FS is increased from 0.5%-1% to 2-3%. The risk is substantially increased to 8% in children with a complex initial FS, i.e. multiple, prolonged or focal, or children with a positive family history of epilepsy.[27-29]

Approximately 9% of children who visited the Children's Hospital with a first FS, including inpatients and outpatients, had febrile status epilepticus (FSE). Two years after the FSE, 5% had developed serious defects and 19% had mild to moderate defects. Remarkably, speech disorders were the predominant defect. The administration of more than two different drugs to terminate the seizure was a statistically significant predictors of sequelae, and a seizure duration of more than 45 minutes was associated with an increased risk of sequelae (borderline significant). It is difficult, however, to make an accurate assessment of the seizure duration from the history.
We know no other study which exclusively addressed FSE children without previous seizures. Inclusion of children with prior (febrile) seizures may reduce the observed risk of sequelae of FSE, because FS children have a favorable prognosis 25 Therefore, we investigated the outcome of only a first FSE.
Forty percent of the patients arrived at the hospital after spontaneous recovery from the FSE (n=23). Once convulsing children have arrived in the hospital, the duration of the seizure and the administered anticonvulsant drugs are recorded. Thus, the number of given medications appeared to be a better predictor than the information (anamnesis) about the duration of a seizure.
Our study was performed retrospectively, so loss of detailed information about the neurological and developmental history of the patients is possible. Also, the assessment of development was performed by different doctors and at different time intervals. Minor previous developmental delay might go undetected.

About 90% of FSE occur as a first seizure.[14,30] Predictors of a lengthy FS could not be found in the literature. In a population based study by Verity et al. 5% of FS children experienced a FSE.[14] Ellenberg found that 6% of FS children in their study population experienced FSE.[26] The frequency of FSE in our patient sample was 9%. The increased number is very likely due to the fact that our study population was taken from a tertiary referral hospital.

Pathophysiological research of prolonged seizures in animal models showed that initially there is a short period of increased cerebral blood flow and metabolic rate, but then cerebral blood flow falls and cerebral oxygen insufficiency develops. This transitional period begins after 20 minutes seizure duration, and permanent brain damage occurs after 60 minutes.[31,32] Damage occurs even in

adequately ventilated animals. Therefore, cell death appearing after 60 minutes is thought to be caused by an excessively increased metabolic rate of ongoing discharging neurons. Pathologic studies of human brains after FSE show signs of ischemic cell damage, necrosis, and atrophy of the involved neuronal structures.[13,31,32]

In one clinic-based study of FSE by Maytal et al.[3], out of 44 FSE patients three (7%) had subsequent afebrile seizures, but no new neurological deficits were observed.[15] Nine children (20%) had preexisting neurological abnormalities, i.e. cerebral palsy and mental retardation; they accounted for the three patients with subsequent afebrile seizures. Also, 14 patients (32%) had had a previous FS, leaving only 21 children without seizures or neurological abnormalities in their history. Other large population based studies found severe sequelae in 0-5% of FSE children.[14] Epilepsy was found in 4-20%, dependent on the occurrence of epilepsy in the parents.[28] One study yielded no IQ deficits nor any sequelae after FSE.[26]
The risk factors for sequelae identified in our study, the number of anti-convulsive drugs and the seizure duration, were in concordance with findings by Aicardi and Maytal.[13,15]

In conclusion, FSE has a potential risk of cerebral damage, as shown in animal studies on protracted seizures and in clinic based studies. In population based studies the risk of sequelae after FSE is very small. Children with sequelae after FSE may be a separate entity, being distinct from the population of children with FS. Preexistent small developmental disorders or a susceptibility to epilepsy might be possible in this category. Minor pre-existent defects, however, were not detected in our study. Follow up for impaired speech development is recommended in children who had FSE.

Future research may determine the prevalence of 'minor' developmental disorders before FSE. Also, the psychomotor development before and after FSE may be assessed and subsequently compared with findings in children with and without FS. However, this would require the development of a large prospective follow-up study. A sample size of 15,000 children would yield 15 to 34 children with a first FSE. This is based on a 3% cumulative incidence of FS, which

yields 450 children with FS, from which 5% (95% CI, 3% - 8%) develop a first FSE.
The costs of such a study seem rather high and raise doubts about the feasibility of determining the risk of FSE and the spectrum of FSE sequelae in the Netherlands.

Familial factors

The occurrence of FS is strongly associated with a positive family history for FS. The value of a detailed family history in the prediction of FS recurrences was determined in chapter 2. The FS recurrence risk was analyzed in relation to the child's family history and in relation to the proportion of first degree relatives that had been affected by FS before. A positive first degree family history was confirmed as a risk factor for FS recurrences. A positive FS history off second or third degree relatives had no additional predictive value. The FS recurrence risk of the index child was found to be proportionally related to the fraction of first degree relatives with a positive FS history. By using this fraction, differentiation is possible between children with low (27%), medium (40%) and high (80%) recurrence risk.

In chapter 3, we studied the risk of FS in relatives of FS children. The risk of FS in siblings of children affected by FS (10%) was more than two times higher than the population risk (4%). The following risk factors for occurrence of FS in siblings were identified: young age at onset of the proband, FS recurrences in the proband, and a positive FS history of one or both parents. A practical model based on these factors was developed to predict FS in siblings according to their attained age. Siblings with two or more risk factors had a 40% risk to develop FS before the age of six years.

Febrile seizures have been observed in several families with Benign Familial Neonatal Convulsions (BFNC), an autosomal dominant inherited convulsive disorder that is linked to chromosome loci 8q24 and 20q11 (chapter 4).[33-35] In one study of six small BFNC families, including three additional relatives with FS only, however, the existence of shared susceptibility genes for BFNC and FS was excluded.[36] We performed a genetic linkage study in one large three-generational FS family with eleven relatives with a history of

FS (chapter 4). The proband of the family in this study was one of a cohort of 142 FS children with families; the identified family was the only FS pedigree that was found suitable for linkage analysis. Linkage of FS with the BFNC loci on chromosome 8q24 and 20q11 was significantly excluded, with lod scores below -2.

The study population has been described in the paragraph 'General aspects'. All consecutive patients were prospectively followed by the same investigators. 100% of contacted parents complied with the study and were interviewed; 92% of the children had complete follow-up. Follow-up was performed by telephone, after a short questionnaire had been send. In other studies, data collected by telephone interviews have been compared with data collected by in-person interview, and were found to be of similar reliability[37,38] In the present study the parents were asked to check the data with the grand parents, if possible.

For our linkage study, a questionnaire was sent to all individual participants for phenotypic classification of FS. At verification of the returned questionnaires, the first-hand information on three second degree and of two affected third degree relatives did not appear to be correct (see table 1; appendix III). This information was obtained from the parents of the proband by means of a structured telephone interview. This method was therefore found to be reliable to obtain histories of first degree relatives, but it was unreliable in more distant relatives.

Because the population prevalence of FS is rather high (up to 4%), FS (family) history of spouses was obtained as well. Another general problem in genetic studies of FS is that the FS gene may not be expressed if a child has no or only low fevers in its susceptible age period, i.e. penetrance below 100%.

Regular occurrence of febrile episodes is normal for young children, and is a result of exposure to infectious agents which had not been encountered yet by their immune system. Most fevers are caused by infections by viruses which are common in the environment; vaccinations are also a common cause of fever in this age group.[39-41] Nevertheless only 2% to 5% of children in Europe and the United States develop FS.[25,42-44] A higher incidence is found in some countries of the Far East, probably due to genetic factors.[45,46] Although fever is necessary for the expression of FS, the develop-

ment of FS seems therefore conditional upon the susceptibility for FS in children in this particular age category.
Familial aggregation of FS has long been a consistent finding.[45,47-49] FS occurrence is not related with social status or income of the parents.[50] FS children in Western Europe have a probability of about 20% of a positive family history (this study)[42,44,50], and FS children with a positive family history of FS have an increased risk of FS recurrences (this study).[30,51]

In a meta-analysis by Offringa et al., a main predictor of FS recurrence was a history of febrile or unprovoked secures in a first degree relative, together with age and seizure history of the index-child and a relatively low temperature at the first seizure.[30] A positive family history remained the only significant predictor after a second recurrence. This relation was confirmed and specified in our study, which demonstrated a dose-response relation between the proportion of first degree relatives affected by FS and the recurrence risk of the proband. Siblings of FS children have an increased risk to develop FS (this study).[41,43,44,49,52] This risk is further increased by young age at onset and recurrences in the proband and by a history of FS in one of the parents (our study). Twin studies yielded a considerably and statistically significantly higher concordance rate of FS in monozygotic twins than in dizygotic twins[53-55], suggesting an important hereditary role in FS susceptibility.

Knowledge of the precise mode of inheritance of predisposition to FS would allow the identification of patients at risk for frequent FS recurrences or epilepsy and the elucidation of pathogenetic mechanisms, which may further increase development of preventive measures.
The population of FS children is probably a genetic heterogenic group. Fifty to 75% of FS patients have a negative family history of FS. In these sporadic instances, the occurrence of FS may be more dependent up on the right stimulus at the right time, with less influence of a genetic susceptibility. At the other hand, this group may have a recessive mode of inheritance, as is found in one epidemiologic study.[47] Others found a polygenic mode more likely.[43,48,49,52] This is in agreement with the results of our family risk study, in which the risk of FS in siblings of children with FS was increased to 10%. An autosomal dominant mode of inheritance was proposed by Rich et al. in families of children with recur-

rent seizures.[55] This is in accordance with Offringa et al., who found that a family history for (a)febrile seizures was the major predictor of more than two FS recurrences.[30] Probably, children with a high recurrence risk are a category with an important familial (genetic) background.
We investigated whether the BFNC-associated genes might be responsible for FS susceptibility in a family with several members affected by recurrent FS. However, our linkage study confirmed the findings of Malafosse et al., who also excluded linkage of FS with the BFNC-locus on chromosome 20q11.[36] Additionally, we excluded linkage of FS to chromosome 8q24.

We conclude that assessment of FS in more distant relatives by means of a standardized interview from the parents has a low reliability. Taking the FS history from all separate relatives and cross checking with information obtained from other relatives and medical records is a more reliable method. The last method is used for phenotyping in genetic linkage studies of FS. Until now, both epidemiologic and genetic studies failed to reveal a definite inheritance pattern of FS. FS appears to be a disease with a heterogeneous genetic background. A multifactorial mode of inheritance seems most probable for the population of FS children at large. Some major genes may be involved in families with many affected relatives or with relatives who had multiple FS recurrences. However, FS pedigrees with a large enough number of affected relatives to perform genetic linkage analysis are very rare. Genetic sib-pair analysis may be a valuable method to identify genetic factors in FS and to localize FS predisposing genes.[56] The sib-pair method investigates the number of shared alleles within sib-pairs at a particular marker locus. Evidence for linkage between the disease locus and the marker locus is found, when the number of shared alleles is significantly greater than expected with non-linkage. At least 100 sib-pairs are required to detect linkage between a codominant genetic marker and a single locus for FS by means of the affected sib-pair method.[57] Candidate loci for this method may be juvenile myoclonic epilepsy (chromosome 6)[58-59], partial epilepsy (chromosome 10q)[60], and progressive myoclonus epilepsy (chromosome 21).[61,62]

Antipyretics and fever

In chapter 6 it was shown that both ibuprofen and acetaminophen produced effective fever reduction in FS children. The short term antipyretic effect of 5mg/kg ibuprofen (4 hours after the first dose) was 0.5°C greater than 10mg/kg acetaminophen (p=0.04). The parents were compliant with 85% of the dosages. Therefore, ibuprofen 5 mg/kg dose 4 times a day yields greater fever reduction than acetaminophen 10mg/kg/dose in FS children.

It has been demonstrated that the resorption of acetaminophen in suppositories varies and leads to unpredictable plasma concentrations. Also, lower drug blood levels are reached and less antipyresis is acquired with suppositories than with syrups in the same dose.[63] Ibuprofen suppositories are not available because of unsatisfactory rectal absorption.[64] A syrup formulation makes fine adjustments of the dose to the child's weight possible. Because over 90 percent of the causes of fever in FS children are upper respiratory tract infections, most of the children tolerate the syrup very well. We choose to compare ibuprofen, a relatively new non-steroidal anti-inflammatory drug (NSAID) with promising antipyretic properties (see below), with acetaminophen, presently still the most used antipyretic in children. Patients with concomitant medication such as antibiotics were excluded. The pathogenesis of fever, and its role in the aetiology of FS is discussed in the introduction chapter of this thesis.

Acetaminophen is a para-aminophenol derivative. It belongs to the group of NSAIDs; it has a demonstrated antipyretic and analgesic effect, and only a minor anti-inflammatory effect.[65] The action of acetaminophen is probably due to a reversible inhibitory effect on the enzyme cyclo-oxygenase, which forms prostaglandin E2. Fever reduction is thought to be a result from central inhibition of prostaglandin E2 formation. Acetaminophen was first prescribed as antipyretic in 1893 by Von Mering. In 1949 para aminophenol was recognized as the major active metabolite in phenacetin, and it became widely used as antipyretic afterwards.[65] Only in 1956, the antipyretic effect of acetaminophen in children was established.[66] In the late fifties it became an over the counter (OTC) product in most countries.[67] After the evidence concerning the association between Reye's syndrome and Aspirin had been established, the use of acetaminophen increased considerably in the 1980s.[68-70] It

is now generally used as the antipyretic of choice for uncomplicated fevers in children.[66]

In the group of propionic acid derivatives, medical practice has longest experience with ibuprofen. It belongs to the group of NSAID's, and has antipyretic, analgesic as well as anti-inflammatory effects. Ibuprofen is a reversible inhibitor of the cyclo-oxygenase enzyme, and thus inhibits prostaglandin E2 production.[65] Ibuprofen has been prescribed in the Netherlands since 1969. Ibuprofen was preferred over acetylsalicylic acid because it had similar anti inflammatory and analgesic effects as Aspirin, but had less gastro-intestinal side effects. The product consists of several isomers of which most the identity and effect are not yet established.[71] Initially, it was mainly prescribed as an analgetic for arthritis, dental pain, dysmenorrhoea and muscle or joint aches. In the last decade, ibuprofen started to be used as antipyretic, and more experience has been gained in children. Ibuprofen syrup formulation was registered in 1982 by the Dutch drug administration, the 'College ter beoordeling van Geneesmiddelen'. Since June 1996, ibuprofen syrup has been approved as an OTC product and may be used in children over six months of age in the Netherlands. Some advise to use ibuprofen as second-line antipyretic therapy.[66]

The pharmacokinetic aspects of ibuprofen and acetaminophen in children have been investigated in several studies (see also table 1; appendix IV). Acetaminophen is rapidly and completely absorbed in the gastro-intestinal tract. Peak plasma levels are reached at 30 to 60 minutes after the initial dose. Acetaminophen is for 60% bound to plasma proteins. It is metabolized in the liver by sulphation and glucuronidation pathways, which predominates in young children.[72] Oxidation has a minor role in therapeutic doses in children.[73,74] The half time of elimination is about two hours.[65] For doses in the therapeutic range, peak maximum blood concentrations (ca. 20 mcg/L) are acquired in 1/2 to 1 hour. The kidneys are responsible for excretion of 95% of its metabolites. Eighty percent of taken ibuprofen is absorbed in the gastro-intestinal tract, of which 99% is bound to plasma proteins. Available formulations are a mixture of different isomers, and the (therapeutic) effect of the individual compounds have not yet been identified.[71] The half time of elimination of ibuprofen is about 1.5 to 2 hours, and peak maximum concentrations (ca. 40 mcg/l) are reached in

about one hour. Ibuprofen is mainly metabolized in the liver through hydroxylation and carboxylation; 99% of metabolites are excreted by the kidneys.

The antipyretic efficacy of ibuprofen and acetaminophen in children is well established. Since 1980 several open studies were conducted which investigated the safety and efficacy of ibuprofen and acetaminophen.[75-81] Mostly single doses of 5-10mg/kg were compared in an unblinded manner. In these trials the tolerability and safety of ibuprofen appeared to be equal to that of acetaminophen, with similar or greater antipyresis with ibuprofen dosage. Since 1985 nine randomized double blind (placebo) controlled trials (RCT's) were published which evaluated the antipyretic activity of ibuprofen and acetaminophen.[82-90] (see also tables 2A and 2B; appendix IV). Five studies are single dose and four are multiple dose. Our study was the only one which included FS children and in which no antibiotics were given. Children with recent FS were either not eligible or not mentioned in the other studies. Most multiple dose studies excluded children who were already on antibiotic treatment, but if needed antibiotics were started during the study period. In the study by Autret et al., children were treated with both an antipyretic drug and an antibiotic.[89]

We performed a quantitative summary of the nine studies mentioned above. The maximal temperature reduction, that is the maximal fall in temperature from base-line (3 to 4 hours after the initial dose) was the most used outcome measure in these studies. Within every study, comparisons of the maximal fever reduction were in agreement with the results of other evaluated endpoints - those are the square of the area under the temperature curve and the mean temperature over time. It was also shown that placebo treatment yielded little but no significant fever reduction in these RCTs. Therefore, we choose the maximal fever reduction per treatment as the measurement to be evaluated in this analysis. The studied treatments were ibuprofen 2.5mg/kg/dose, 5mg/kg/dose and 10mg/kg/dose and acetaminophen 10mg/kg/dose. The mean maximal temperature reduction was calculated, weighed for the number of patients in each individual study. (A calculated pooled difference between these treatments, as is commonly done in meta-analyses, would yield a highly unreliable result, because

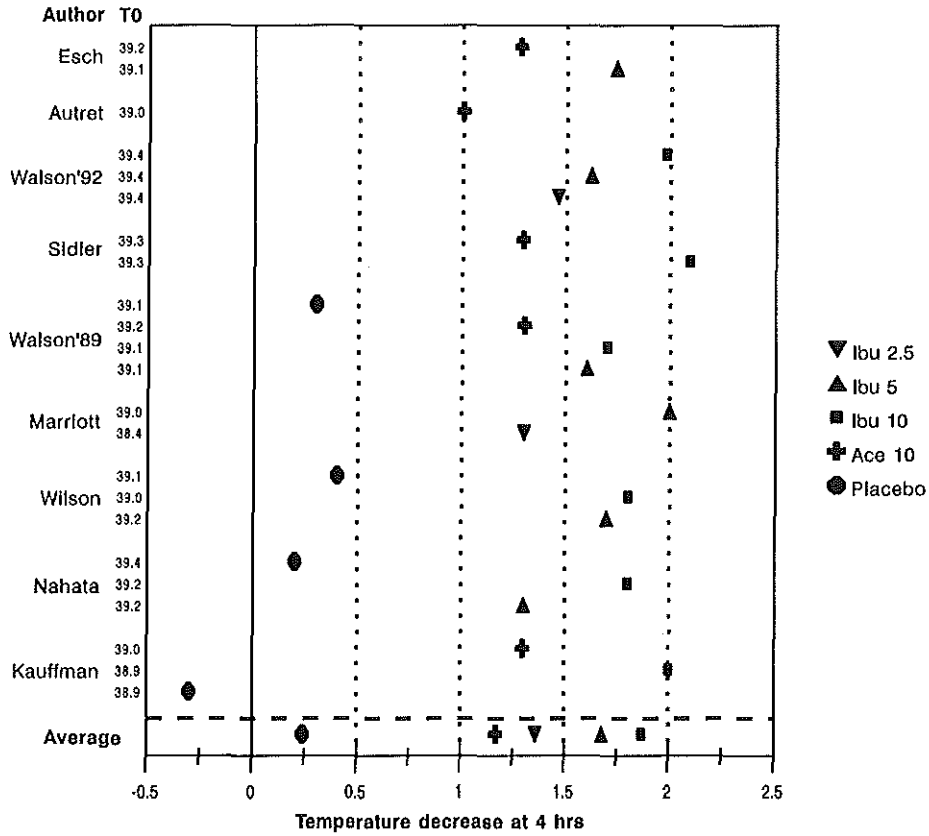

Figure – Mean temperature decrease at 4 hours after the first dose according to study (indicated by first author and mean initial temperature T0) and medication dose. From top to bottom are shown the results of nine studies and the average estimate.

only two of the available studies compared the same acetaminophen and ibuprofen doses.)

An overview of the antipyretic effects of ibuprofen and acetaminophen in the respective RCTs is given in the figure above. From top to bottom are shown four multiple dose studies and five single dose studies. Ibuprofen was generally the most effective treatment if compared with acetaminophen in equal doses. Only ibuprofen doses 2.5, 5, and 10mg/kg and acetaminophen 10mg/kg are shown (for more details, see tables 2A and 2B; appendix IV). Summary results are displayed at the bottom of the figure. Antipyresis with ibuprofen showed a dose-response relationship.

Antipyresis with acetaminophen 10mg/kg was 1.17°C (SD 0.14) and less than with ibuprofen 2.5 (1.36°C, SD 0.8), 5 (1.68°C, SD .18), and 10mg/kg/dose (1.87°C, SD 0.14) The mean base-line temperatures in the study of Marriott et al. were lower than in the other studies.[84] Exclusion of this study from the analysis yielded no significant difference of the summarized outcome measure. The average antipyretic effect of acetaminophen without the study of Autret et al., who combined antibiotic with antipyretic treatment, is 1.29°C. This comes near to the average effect of ibuprofen 2.5 mg/kg/dose.

Adverse effects of ibuprofen and acetaminophen in the studies discussed above were infrequent (see also tables 2A and 2B; appendix IV). Some mild gastro-intestinal complaints, mild respiratory complaints, behavioral disturbances such as irritability, febrile seizures, rash, epistaxis and hypothermia were seen. However, most adverse effects were disease related. Altogether, mild drug related side effects were seen with ibuprofen treatment in 2% of the cases (gastrointestinal complaints, rash, hypothermia and epistaxis) and with acetaminophen in 3% of the cases (gastro-intestinal complaints, hypothermia). A total number of about 800 patients were included in these trials.
A large practitioner-based trial on the safety of ibuprofen and acetaminophen for treatment of fever in children included 84,000 children.[91] With both drugs, no side effects leading to hospital admissions were observed (i.e. serious bleedings, renal failures and anaphylactic reactions). Only mild gastro-intestinal bleedings were observed in four children receiving ibuprofen, for which hospital admission had not been necessary. Gastro-intestinal bleedings were seen in 4 of 55,785 children treated with ibuprofen (risk: 7/100,000) and in none of 28,130 children treated with acetaminophen (risk: 0/100,0000); the difference was not statistically significant. Neither were significant differences found in the incidence of leucopenia[92] Less serious adverse events (abdominal pain, asthma, erythema) were also recorded, but they were not reviewed by the trial boarding committee on their relation with the drugs.

Toxicity and poisonings with acetaminophen occurs with ingestion of more than 125-150mg/kg.[68] Children develop vomiting, hepatoxicity with centrilobular necrosis, and possibly renal abnormalities.[72,73] Symptoms of toxicity with acetaminophen poisoning in children are generally less serious than in adults, which mostly

have suicidal poisonings. Probably less toxic compounds are formed in children; this may be due to the utilization of different metabolic pathways. The compounds may be metabolized by the pathway of sulphation, which may be predominant over glucuronidation in young children[72], or a more efficient clearance of the toxic compounds may exist.[68,74,93] However, several fatal poisonings leading to hepatic necrosis with acetaminophen have been described in children.[94-96] Most were caused by parents giving too high dosages and too long.[72] Toxic levels of >150 mcg/ml are reached at 4 hours after ingestion, corresponding to a half-life of 4 hours, i.e. more than 10 times the therapeutic dose.[68,74] Toxicity of ibuprofen may occur with ingestion of more then 100 mg/kg.[97] Mild CNS depression and gastro-intestinal discomfort may be the only symptoms of large overdoses of ibuprofen. Some cases of more serious symptoms like coma and hypotension, apnoea and cyanosis and acute renal failure have occurred.[97] Only one case fatality of ibuprofen overdose has been described.[97] Overdoses resulting in acidosis, seizures, and coma are reversible when treated adequately with supportive care. Toxic levels (>100 mcg/ml at 1 hour after ingestion) are reached with ingestion of more then 100 mg/kg, i.e. more than 10-20 times the therapeutic dose.[97]

In conclusion, our study showed that most parents, after appropriate instruction, were able to give the complete medication dose (syrup) to their child. Most parents adhered to the protocol and both antipyretic drugs were well tolerated by the children. Ibuprofen and acetaminophen reduced the average temperature below 38.5°C, and the temperature remained there during treatment. The short term antipyretic effect of ibuprofen 5mg/kg/dose was significantly greater than that of acetaminophen 10mg/kg/dose. A dosage recommendation of 5mg/kg/dose for ibuprofen may be given for fever reduction in children with a history of FS. From the quantitative literature review it may be concluded that a higher dose of acetaminophen, e.g. 12.5mg/kg, is necessary to acquire an antipyretic effect equal to that acquired with ibuprofen 5mg/kg/dose.[83] In case of persistent and high fevers resistant to ibuprofen 5mg/kg/dose, the dose may be increased to 10mg/kg/dose. We calculated the mean maximal temperature reduction of the respective doses of ibuprofen and acetaminophen in this quantitative review. These results are no direct measure for the potential value of these drugs in the prevention of FS recurrences.

Nevertheless, there was a fairly consistent correlation between the maximal temperature decrease and the other used outcome measures in the evaluated RCTs.

The incidence of adverse effects with ibuprofen and acetaminophen is low. The development of adverse effects has no clear relation with the height of the dose in the therapeutic range.
Considering the costs, both drugs are of equal cost per mg (about Dfl. 8.00 per 2000mg for acetaminophen 24mg/ml and ibuprofen 20mg/ml).[98] In a Dutch pharmacy, a bottle of 100ml acetaminophen syrup costs Dfl. 8.95, the cost of a bottle of 100ml ibuprofen syrup is Dfl. 6.95. Both drugs have a shelf life of several years in the closed bottle; after opening it will keep 2-3 weeks. Because one bottle can generally be used for one febrile period only, the taking of ibuprofen is about 20% cheaper as of acetaminophen.

Antipyretics and prevention of febrile seizure recurrence

In our study on the potential prevention of FS recurrences by antipyretic drugs (chapter 7), no effect of ibuprofen or acetaminophen during fever for the prevention of FS recurrences was demonstrated in an intention-to-treat analysis. When only those children were included who actually received their antipyretic treatment on time, a potential preventive effect of around 50% was found. For this analysis, only a small delay between the onset of the fever and the administration of the antipyretic drug was permitted.
Several limitations need to be taken into account. Firstly, there was no randomization to treatment in this study. We merely compared a randomized clinical trial of two antipyretic drugs with a natural history study without treatment as a control group. The treatment group was studied at a later time (years 1992 and 1993) than the control group (years 1990 and 1991). However, the intention to treat analysis yielded no difference in preventive effect. A possible selection bias would likely increase the preventive effect of the treatment group. Therefore, a major difference in patient selection between both groups does not seem probable in the intention-to-treat analysis. The results of the on-treatment analysis, however, should be taken cautiously, and are likely to give an overestimation of the preventive effect of antipyretic treatment.

A small risk of epilepsy after FS exists; no significant reduction of the risk of epilepsy by FS recurrence prophylaxis with antiepileptic drugs or diazepam is found.[29,99] In a recent study, no differences were demonstrated in long term neurological outcome between FS children who had received valium prophylaxis and those who had not.[99] However, prevention of FS recurrences is still worthwhile because FS recurrences in itself are a terrifying event. Hospital visits and (laboratory) investigations lead to a considerable consumption of health care resources. Moreover, lengthy FS recurrences have a small but evident risk of (serious) neurological sequelae. Trials with diazepam in children with average risk profile showed little or no effect[5,100,101], but the preventive efficacy increases in children with one or more risk factors for recurrence.[10] Therefore, preventive therapy with antipyretics may be useful in children with a high recurrence risk. In our study this was about 50% of the FS patient population.

To date, antiepileptic drugs are not regularly used for FS recurrence prophylaxis because of considerable cognitive side effects, while the preventive effect is modest.[102] Only children with very frequent recurrences may benefit from valproate prophylaxis.[103] The use of valium has been studied in FS children in the last decade. Three double blind RCTs of valium administered orally during fever have been published.[5,100,101] The preventive effect of this treatment was about 50% in one study (relative risk 0.56)[100], the other two studies demonstrated no (significant) preventive effect.[5,101] Up to 40% of patients had side effects like ataxia, lethargy and irritability. It is important to note that the authors contributed the lack of effect or at least part of it to poor compliance: medication had been given too late to respectively 68 children (68 of 113 recurrences) and to 25 children (25 of 33 recurrences).[5,100] The main reasons were that parents did not take temperature in case of illness – convulsions being the first manifestation of fever – and parental omission to give treatment. However, Knudsen demonstrated a considerable effect of intermittent prophylaxis in an open trial (overall recurrence risk dropped from 39% to 12%) with rectal valium.[104] Only 4% of fevers was not detected by the parents before a recurrence.

According to current knowledge, the immediate antecedent of FS development is an elevated body temperature in a susceptible child. It was reported that febrile children with FS had significantly

higher temperatures than febrile children without FS (39.4°C versus 38.8°C).[105] Thus, reduction of fever by antipyretic drug treatment seems an appropriate way to pursue prevention of FS recurrence.[105,106] Furthermore, antipyretics are safe and reliable drugs, and their efficacy has been proven. They are cheap and readily available. In our study, most common infections were of viral origin, and no intracranial infections occurred. In only 9% of the children antibiotic treatment was indicated.

Previously, two randomized studies evaluated antipyretic treatment for prevention of FS recurrences.[101,107] The first study suggested a minor reduction of FS recurrences by antipyretic treatment. No control group was included, however.[107] The other study investigated the combined effect of valium and acetaminophen, and demonstrated no preventive effect of antipyretic acetaminophen use.[101] However, the base-line recurrence risk of the study population was low, and acetaminophen rescue medication was given to children with temperatures above 40°C. In this study, in which we compared recurrence risks between children offered antipyretic treatment and children who were not offered antipyretic treatment, no preventive effect was found in the intention-to-treat analysis. A potential preventive effect of around 50% was found in an on-treatment analysis. The important assumption in the last approach is that there is only a minimal delay between the onset of the fever and the administration of the antipyretic drug. The effectiveness of antipyretic prophylaxis seems therefore to be dependent on early notice of fever by the parents or guardians and prompt administration of the drug. This may be guaranteed by clear and thorough instruction of the parents or guardians on adequate administration of the antipyretic medication which needs to be readily available at home. When these practical requirements are met, effective prophylaxis of FS recurrences by means of intermittent treatment with antipyretic drugs may be possible. The actual preventive effectiveness of such a treatment remains to be determined in a randomized clinical trial.

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Summary
Samenvatting
9

Summary

In this thesis, several studies on the relation between familial risk factors and the susceptibility for febrile seizures (FS) and FS recurrences are described, and one study on the outcome of febrile status epilepticus (FSE). Also, the use of the antipyretic drugs ibuprofen and acetaminophen in FS children is studied, to determine their antipyretic efficacy and effectiveness for prevention of FS recurrences.

The introduction, **chapter 1**, gives a description of the clinical presentation and epidemiology of FS and an overview of the current knowledge of the etiology. FS is a common and generally benign seizure disorder in childhood. The mechanism by which fever causes FS is not known at present. The occurrence of FS depends on age, seizure susceptibility and the height of the fever. Because familial aggregation of FS is a consistent finding in epidemiologic research, the susceptibility to FS is likely to be genetically determined. A positive FS family history is also a major risk factor for FS recurrence.
After acute management, the risk of FS recurrence, which is about 30%, is the main problem. Although the prognosis of FS recurrences is good, their occurrence is a frightening event for parents. The management of children having a history of FS at a new febrile episode remains controversial.

In **chapter 2**, we determined the value of a detailed family history for the assessment the risk of recurrence of FS. One hundred and fifteen children who visited the emergency room of an academic children's hospital were studied prospectively. The recurrence risk of FS was analyzed in relation to the child's family history and the

proportion of relatives affected by FS using Kaplan-Meier estimates and Cox proportional hazard models. A first degree family history positive for FS (parents or siblings affected by FS) increased a child's two year recurrence risk from 27 to 52%. No significant increase of recurrence risk for FS was found in children with second degree relatives (grandparents and uncles/aunts) or cousins only affected by FS: risks were 27, 40, and 83% in children whose proportion was 0, 0 to 0.5, and ³0.5 respectively. Analysis of the recurrence risk in relation to a weighted proportion, adjusted for the attained age and sex of first degree relatives, showed similar results. We concluded that application of the proportion of first degree relatives affected by FS generates a more differentiated assessment of the recurrence risk of FS.

To quantify the risk of FS in relatives of children with FS and to predict the risk of FS in siblings, we calculated cumulative risks of FS in first degree relatives of 129 children with FS in **chapter 3**. The study was conducted as a prospective follow-up study of FS children at the outpatient clinic of the Sophia Children's Hospital in Rotterdam.
Thirteen parents and 12 siblings had experienced FS, accounting for a cumulative incidence of 7% at six years of age. The incidence of FS was increased in relatives of children with recurrent FS (12%). The incidence of FS in siblings of FS children in our study was 10%. This is more than twice the average risk of FS in the Dutch population (4%). A positive FS history in a parent, young age at onset in the proband, and recurrences in the proband yielded respectively 25%, 17% and 16% risks of FS in siblings and were selected in a multivariable prediction model. If two or more of these risk factors were present, the risk of West European siblings to develop FS before the age of six years was 46% (hazard ratio 5.4).
We conclude that the risk FS in siblings of children with FS is increased. The age attained risk of a first FS can be estimated using a practical model incorporating three readily available risk factors.

A genetic background for FS has been suspected for several years, but the mode of inheritance is still unknown, and no FS gene has been identified yet. FS occurs frequently in children with previous Benign Familial Neonatal Convulsions (BFNC), an autosomal dominant trait in early childhood. We investigated whether BFNC

might be or might be not causing (part of) susceptibility for FS.
Chapter 4 describes a genetic linkage analysis in a three-generational FS family with multiple affected relatives (n=8). Markers for the chromosomal regions 8q24 and 20q11 chromosomal regions, implied in BFNC, were tested for linkage with FS. Linkage with the 8q24 and the 20q11 loci of BFNC with FS susceptibility was significantly excluded in this family. Therefore, it seems improbable that BFNC genes cause FS susceptibility.

Chapter 5 contributes to the current literature on the outcome of febrile status epilepticus (FSE). The neurological outcome after a first FSE was retrospectively studied in 57 children. Patients were aged six to 57 months at first seizure occurrence and had had no previous seizures or neurological abnormalities. Twelve children (24%) had subsequent neurological sequelae varying from speech deficit (n=9) to severe neurological sequelae and epilepsy (n=3). Speech deficit was detected after a mean period of six months. The most important predictors for sequelae were the number of different drugs needed for seizure termination and the duration of the seizure.
We recommend that children with FSE should be followed up for at least one year so that potential speech disorders can be detected and intervention can be recommended.

Although many children with FS use antipyretic medication during fever, the antipyretic and preventive effect of this medication in FS children had not been established yet. In **chapter 6**, the antipyretic efficacy of ibuprofen syrup and acetaminophen syrup in children with a history of FS is compared in a randomized, multiple dose, double-blind, crossover trial of ibuprofen (5mg/kg/dose) and acetaminophen (10mg/kg/dose).
Seventy outpatient children (mean age 2.1 years) who had visited the hospital with FS were randomized to treatment at a fever of 38.5°C or greater. The study medication was given every 6 hours for the duration of one to three days. Rectal temperatures were recorded 0, 2, 4, 6, 12 and 24 hours after the first dose. The temperature 4 hours after the first dose, the mean temperature during treatment and the highest temperature during treatment were the evaluated main outcome measures.
Ibuprofen lowered the initial temperature from 39.1°C to a mean temperature of 37.7°C during treatment; acetaminophen lowered the initial temperature from 39.2°C to 38.0°C. Ibuprofen reduced

fever 0.50°C more than did acetaminophen at 4 hours after the first dose. The mean temperature during treatment and the highest temperature were lower during ibuprofen treatment (not statistically different). In 22 patients a second fever was treated with the opposite medication than the first. In the crossover analysis the respective results of the parallel analysis were confirmed.
We conclude that ibuprofen and acetaminophen are effective antipyretics in children with a history of FS. Ibuprofen 5mg/kg/dose yielded greater fever reduction than did acetaminophen 10mg/kg/dose at 4 hours after the first dose.

In **chapter 7**, we performed an assessment of the potential prevention of FS recurrences by antipyretic medication during fever. We therefore determined the incidence of FS recurrence in 109 children who were offered treatment with ibuprofen or acetaminophen syrup during fever, and in 103 children who were not offered antipyretic treatment. The Children had FS between one and three years of age and were treated at the outpatient department of the Sophia Children's Hospital, Rotterdam. Recurrences were prospectively recorded in both study groups.
In an intention-to-treat analysis, the number of recurrences per fever and the cumulative incidence of any recurrence were compared between the treatment groups. An on-treatment analysis compared the number of recurrences per fever between those children in the treatment group who actually received medication and the control group.
In the intention-to-treat analysis no preventive effect of antipyretic treatment could be demonstrated. The recurrence risk per fever was 15% in the treatment group and 12% in the control group, the relative risk was 1.3 (95% CI, 0.7 to 2.4). Also the relative risk of any recurrence for treatment was close to one (RR 1.1; 95% CI, 0.7 to 1.8). In the on-treatment analysis however, antipyretic treatment resulted in a recurrence risk per fever of 7%, the relative risk was 0.5 (95% CI, 0.2 to 1.3; 12% recurrences in the reference category).
These results indicate that the feasibility of intermittent prophylaxis of FS recurrences with antipyretic medication remains uncertain. The effectiveness of such a prophylactic treatment is very much dependent upon a prompt administration of these drugs when a child gets a febrile illness, as demonstrated in the on-treatment analysis. A double blind randomized controlled trial of

antipyretic versus placebo treatment during fever is needed to determine the preventive effect of such a treatment.

In the discussion section, **chapter 8**, the results of the studies are discussed and reviewed in light of the literature. Additionally, the pharmacological and clinical properties of the antipyretic drugs ibuprofen and acetaminophen were discussed in more detail, and a semi-quantitative review of their antipyretic action is performed. Suggestions for future research are given.

In conclusion, our study confirms the importance of familial factors for the predisposition of febrile seizure (FS), and provides tools for a more differentiated prediction of FS recurrences in children with previous FS and for the prediction of a first FS in siblings. Genetic linkage of FS susceptibility with the 8q24 and 20q11 loci implied in benign familial neonatal convulsions was excluded in one large family of several members with recurrent FS. A multifactorial mode of inheritance with genetic heterogeneity of several major susceptibility genes is probable for the FS patient population at large.
Children with a febrile status epilepticus as their first FS have an increased risk of sequelae. We found an impaired language development in 24 percent of patients. This has implications for the follow-up of these patients.
Ibuprofen and acetaminophen proved to be effective antipyretic agents in children with a history of FS. The short term antipyretic effect of ibuprofen 5mg/kg was greater than that of acetaminophen 10mg/kg. Prompt administration of antipyretic drugs to febrile children with previous FS may prevent 50 percent of FS recurrences.

Samenvatting

In dit proefschrift worden verscheidene studies over kinderen met koortsconvulsies beschreven (koortsconvulsies wordt verder afgekort als FS, voor het Engelse 'Febrile Seizures'). We onderzochten de relatie tussen familiaire risicofactoren en de gevoeligheid om FS (en FS recidieven) te ontwikkelen. Tevens bestudeerden we het optreden van neurologische restverschijnselen na febriele status epilepticus. Ten slotte bestudeerden we de koortsverlagende werking van de antipyretica ibuprofen en paracetamol bij kinderen met FS in de voorgeschiedenis en de potentiële preventieve werkzaamheid van deze medicijnen op FS recidieven.

De introductie, **hoofdstuk 1**, beschrijft de symptomatologie en epidemiologie van FS en de huidige kennis van de etiologie. Het mechanisme waardoor bij kinderen met koorts koortsstuipen optreden is nog niet bekend. Familiaire aggregatie van FS is een constante bevinding bij epidemiologisch onderzoek, zodat de gevoeligheid voor deze aandoening waarschijnlijk erfelijk bepaald is. Een andere aanwijzing hiervoor is dat een positieve familie-anamnese voor FS de belangrijkste risicofactor voor het ontwikkelen van recidieven is. Na het beleid op de spoedeisende hulp blijft het mogelijke optreden van recidiefconvulsies het voornaamste probleem. De kans voor een kind met FS om een recidief te ontwikkelen is gemiddeld 30%. De prognose van recidieven is goed, maar het optreden ervan is meestal angstwekkend voor de ouders. De behandeling van kinderen met FS in de voorgeschiedenis wanneer zij koorts ontwikkelen blijft vooralsnog onduidelijk.

In **hoofdstuk 2** wordt een prospectieve vervolgstudie van 115 kinderen, die het academisch kinderziekenhuis in verband met FS bezochten, beschreven. Deze studie werd uitgevoerd om de waarde te bepalen van een gedetailleerde familie-anamnese ter voorspelling van recidiverende FS. De tweejaars cumulatieve incidentie van FS-recidieven werd geanalyseerd in relatie met de familie-anamnese en met de proportie van met FS aangedane eerste graad verwanten. Een positieve eerstegraads familie-anamnese (ouders en broers of zussen maakten ook FS door) verhoogde het risico om een recidief te krijgen van 27 naar 52%. Er werd geen significante verhoging gevonden bij kinderen met alleen een positieve anamne-

se in tweedegraads verwanten (grootouders en ooms of tantes) of in neefjes of nichtjes.
Het herhalingsrisico was significant gecorreleerd met de proportie van met FS aangedanen in de eerste graad: de kansen waren achtereenvolgens 27, 40 en 83 procent bij de kinderen van wie deze proportie 0, tussen 0 en 0.5, en 0.5 of hoger waren. De conclusie van dit hoofdstuk is dat men met behulp van de proportie van met FS aangedanen in de eerste graad tot een meer gedifferentieerde bepaling van het risico van recidiverende FS kan komen.

Om de grootte van het risico op FS in verwanten van kinderen met FS te bepalen, en met name de kans op FS in broers of zussen, berekenden we de cumulatieve incidenties van FS in eerstegraads verwanten van 129 FS kinderen in **hoofdstuk 3**. De studie werd uitgevoerd als een prospectieve vervolgstudie van kinderen die verschenen waren met FS op de polikliniek van het Sophia Kinderziekenhuis te Rotterdam. Dertien ouders en 12 broers of zussen hadden in het verleden een FS doorgemaakt, wat een cumulatieve incidentie van 7 procent op zesjarige leeftijd opleverde. De frequentie van FS was verhoogd in verwanten van kinderen met FS recidieven (12%). De frequentie van FS in broers of zussen van FS kinderen in onze studie was 10 procent; dit is meer dan twee maal zo hoog als de gemiddelde kans op FS van kinderen in de Nederlandse populatie (4%). Een positieve familie-anamnese voor FS in een ouder, jonge leeftijd van de proband bij de eerste FS, en recidieven bij de proband resulteerden in respectievelijke cumulatieve incidenties van een eerste FS van 25, 17 en 16 procent in broers of zussen. De genoemde risicofactoren werden geselecteerd in een multivariaat predictiemodel. Bij aanwezigheid van twee of meer risicofactoren was het risico op FS in West Europese kinderen 46% (RR 5.4). De conclusie is dat het risico op FS in broers of zussen van kinderen met FS is verhoogd. Het leeftijdsgerelateerde risico op een eerste FS kan bepaald worden met gebruikmaking van een praktisch model dat de drie bovengenoemde risicofactoren gebruikt, die direct bij de hand zijn.

Sinds lang neemt men aan dat FS een erfelijke achtergrond heeft, maar het overervingspatroon is nog onduidelijk en er is nog geen gen geïdentificeerd. FS komt relatief vaak voor bij kinderen met Benigne Familiaire Neonatale Convulsies (BFNC) in de voorgeschiedenis, een autosomaal dominant overervende aandoening van convulsies op de zuigelingenleeftijd. In **hoofdstuk 4** hebben we onder-

zocht of BFNC wellicht (een deel van) de gevoeligheid voor FS veroorzaakt. Daarvoor werd een genetisch koppelingsonderzoek uitgevoerd in een grote FS-familie van drie generaties met meerdere aangedanen. De markers voor de chromosomale loci 8q24 en 20q11, zoals geïmpliceerd in BFNC, werden getest op koppeling met FS. Linkage van de 8q24 en 20q11 loci met FS werd in deze familie significant uitgesloten. Betrokkenheid van de BFNC genen bij FS lijkt dus onwaarschijnlijk.

In **hoofdstuk 5** worden de gevolgen van status epilepticus bij koorts (FSE) besproken. De neurologische uitkomst na een eerste FSE werd retrospectief bestudeerd in 57 patiënten. De kinderen waren tussen de 6 en 57 maanden oud bij het optreden van de FSE en zij hadden geen convulsies in de voorgeschiedenis of eerder bestaande neurologische afwijkingen. Vierentwintig procent van de patiënten (n=12) hadden neurologische restverschijnselen, variërend van spraakachterstand (n=9) tot ernstige neurologische retardatieverschijnselen en epilepsie (n=3). Spraakstoornissen werden gemiddeld zes maanden na de FSE ontdekt. De meest belangrijke risicofactoren voor restverschijnselen waren het aantal verschillende medicijnen dat nodig was voor beëindiging van de status epilepticus en de duur van de status. Wij adviseren om kinderen na een FSE ten minste een jaar te controleren, zodat eventuele spraakstoornissen opgespoord en behandeld kunnen worden.

Hoewel veel kinderen met FS al behandeld worden met antipyretische medicijnen als zij een ziekte met koorts doormaken, is de koorstverlagende werking van deze medicijnen nog niet eerder bestudeerd bij kinderen met FS. In **hoofdstuk 6** wordt de koortsverlagende werking van ibuprofen en paracetamolsiroop in kinderen met FS in de voorgeschiedenis beschreven in een gerandomiseerde, dubbelblinde, crossover trial met meerdere doses van ibuprofen (5mg/kg/dosis) en paracetamol (10mg/kg/dosis).
Zeventig poliklinische patiënten die het ziekenhuis hadden bezocht met een FS werden bij het optreden van 38.5 graden Celsius koorts of meer gerandomiseerd (gemiddelde leeftijd 2.1 jaar). De studiemedicatie werd elke 6 uur gedurende twee tot drie dagen gegeven. De rectale temperatuur werd op 0, 2, 4, 6, 12 en 24 uur na de eerste dosis gemeten. De temperatuur 4 uur na de eerste dosis, de gemiddelde temperatuur gedurende behandeling en de hoogste temperatuur gedurende behandeling werden geëvalueerd.
Ibuprofen verlaagde de aanvangstemperatuur van 39.1°C tot een

gemiddelde temperatuur van 37.7°C gedurende behandeling; paracetamol verlaagde de aanvangstemperatuur van 39.2°C naar 38.0°C. Ibuprofen gaf 0.50°C meer reductie van de koorts dan paracetamol op 4 uur na de eerste dosis. De gemiddelde temperatuur en de hoogste temperatuur waren lager tijdens behandeling met ibuprofen (niet statistisch significant). In 22 patiënten werd een tweede koortsperiode behandeld met de andere studiemedicatie. In de crossover analyse werden de resultaten van de parallel analyse bevestigd.
We concluderen dat ibuprofen en paracetamol effectieve antipyretica zijn bij kinderen met een voorgeschiedenis van FS. Ibuprofen 5mg/kg/dosis veroorzaakte vier uur na de eerste dosis meer koortsverlaging dan paracetamol 10mg/kg/dosis.

In **hoofdstuk 7** wordt een studie beschreven waarin we de potentiële preventie van recidief koortsconvulsies door behandeling met antipyretica tijdens koorts bepaalden. Daartoe bestudeerden we het optreden van FS-recidieven in 109 kinderen die behandeling met ibuprofen of paracetamol gedurende een koortsperiode kregen aangeboden, en in 103 kinderen die geen antipyretische behandeling kregen aangeboden. De geïncludeerde kinderen hadden tussen hun eerste en derde jaar een FS gehad en waren daarvoor op de polikliniek van het Sophia Kinderziekenhuis te Rotterdam geweest. De beide behandelingsgroepen werden prospectief vervolgd op het krijgen van FS recidieven.
In een intention-to-treat analyse werden het aantal recidieven per koortsperiode en het risico op één of meerdere recidieven vergeleken. Een on-treatment analyse vergeleek het aantal recidieven per koortsperiode tussen de kinderen die de studiemedicatie op tijd kregen toegediend en de controlegroep.
In de intention-to-treat analyse werd geen beschermend effect van antipyretische behandeling aangetoond. Het risico op een recidief was 15% in de behandelingsgroep en 12% in de controle groep, het relatieve risico was 1.2 (95% CI, 0.7 - 2.4). Ook het relatieve risico op een of meer recidieven bij behandeling lag dicht bij één (RR 1.1; 95% CI, 0.7 - 1.8). In de on-treatment analyse echter, resulteerde antipyretische behandeling in een recidiefkans van 7% per koortsperiode. Bij een recidiefkans van 12% in de controle groep was het relatieve risico tijdens behandeling zodoende 0.5 (95% CI, 0.2 - 1.3).
Deze resultaten geven aan dat de beschermende werking van het intermitterende gebruik van antipyretica voor de profylaxe van FS-

recidieven in de praktijk onzeker is. De effectiviteit van een dergelijke behandeling hangt sterk af van een onmiddellijke toediening van de medicatie als het kind koorts ontwikkelt, zoals aangetoond is in de on-treatment analyse. Een dubbelblind gerandomiseerde placebogecontroleerde trial van antipyretica bij koorts dient uitgevoerd te worden om de preventieve werkzaamheid van een dergelijke behandeling te bepalen.

In de discussie, **hoofdstuk 8**, worden de resultaten van de voorgaande studies bediscussieerd en besproken in het licht van de literatuur. Tevens worden de farmacologische en klinische eigenschappen van de koortswerende medicijnen ibuprofen en paracetamol in meer detail beschouwd en wordt een semi-kwantitatief overzicht van de gepubliceerde studies naar de antipyretische werkzaamheid gegeven. Tevens worden suggesties voor aanvullend onderzoek gegeven.

Concluderend bevatten de vermelde studies in dit proefschrift aanwijzingen voor een familiaire predispositie van koortsconvulsies. Er worden instrumenten aangereikt voor een gedifferentieerde voorspelling van het optreden van FS-recidieven, en van FS in broers en zussen van kinderen met FS. Genetische koppeling van FS met de chromosomale regio's 8q24 en 20q11, de loci geïmpliceerd in Benigne Familiaire Neonatale Convulsies, werd uitgesloten in een grote familie. Een multifactoriële wijze van overerving met genetische heterogeniteit van verscheidene 'gevoeligheidsgenen' lijkt waarschijnlijk voor de populatie van FS-kinderen als geheel. Tevoren gezonde kinderen met een status epilepticus bij koorts hebben een verhoogde kans op restafwijkingen. Vierentwintig procent van de kinderen in onze studie hadden spraakstoornissen ontwikkeld. Dit heeft implicaties voor het vervolgbeleid.
Van ibuprofen en paracetamol werd aangetoond dat zij effectieve koortswerende middelen zijn in kinderen met FS in de voorgeschiedenis. Het antipyretisch effect op korte termijn van ibuprofen 5mg/kg was groter dan dat van paracetamol 10mg/kg. Directe toediening van antipyretica bij koorts aan kinderen die FS hebben doorgemaakt heeft een mogelijke reductie van 50% van het aantal recidieven tot gevolg.

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Publications and manuscripts based on the studies described in this thesis

Chapter 2

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Chapter 3

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Chapter 4

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Chapter 5

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Chapter 6

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Chapter 7

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Dit proefschrift is het resultaat van de inspanning van zeer velen, en in ieder geval van diegenen om wie het onderzoek allemaal draaide: de kinderen met koortsstuipen, en hun ouders. Mijn eerste dank gaat dan ook uit naar alle kinderen en ouders die meegewerkt hebben aan dit onderzoek. Tevens wil ik de familie bedanken die heeft meegewerkt aan het erfelijkheidsonderzoek. Het spreekt vanzelf dat dit onderzoek zonder uw medewerking niet tot stand was gekomen.

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Dr H.A. van Steensel-Moll, co-promotor, beste Henriëtte, jij zorgde ervoor dat ik dit project tot een goed einde heb gebracht. Jouw enthousiasme en energie waren voor mij enorm motiverend. Jij stuurde me in de juiste richting wanneer ik met al te hooggegrepen of onrealistische ideeën aankwam, en gaf me de bemoediging die ik nodig had als het allemaal niet zo liep als ik wel graag had gewild. Ook de praktische hand- en spandiensten voor het onderzoek, die je naast je baan en je gezin hebt geleverd, stel ik zeer op prijs.

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Dank ben ik verschuldigd aan mijn eerste promotor Prof. Dr Ir J.D.F. Habbema. Beste Dik, ik stel de door jou verleende gastvrijheid en toegang tot de faciliteiten van het Centrum voor Klinische Besliskunde zeer op prijs. Naast het opdoen van de nodige methodologische kennis, kon ik ook rustig schrijven, wat voor de afronding van het promotie-onderzoek essentieel was. Ook dank ik je voor je kritische commentaar op de manuscripten.

Prof. Dr H.K.A. Visser, ik wil u van harte bedanken dat u op hebt willen treden als tweede promotor, en voor het commentaar dat u leverde op dit proefschrift.

Tevens wil ik Prof. Dr D. Lindhout, Prof. Dr H.J. Neijens en Prof. Dr A. Hofman bedanken dat zij in de leescommissie wilden plaatsnemen, het manuscript in de kerstvakantie hebben willen doornemen, en zo vlot hun beoordeling hebben gegeven.

Naast de eerder genoemden wil ik ook de co-auteurs Martin Offringa, Marjolein Berger, Cock van Duijn, Arno Hoes, Dicky Halley en Bart Janssen bedanken voor hun kritische en opbouwende commentaar tijdens het schrijven van de artikelen, die de basis vormden van dit proefschrift.

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Veel dank ben ik verschuldigd aan Rubia Ramlal, Hannie Groenendijk, Manuella van Dijken en Mona Richter voor het verzamelen en/of invoeren van data.

Ook wil ik bedanken Henriëtte van Vuuren en Marja Suur, die de bloedafnames deden voor het genetische koppelingsonderzoek. Ook wil ik graag alle medewerkers van het Medisch Archief en de Medische Codering in het Sophia Kinderziekenhuis bedanken, voor hun hulp bij het opsporen van patiëntendossiers en het uitdraaien van nieuwe patiëntenbestanden.

De arts-assistenten op de Polikliniek Algemene Kindergeneeskunde van het Sophia Kinderziekenhuis wil ik bedanken voor het aanmelden van patiënten, en de dienstdoende kinderartsen voor de ver-

leende supervisie bij het beoordelen van de kinderen met koorts-convulsies

Alle verpleegkundigen van de Spoedeisende Hulp en de Polikliniek Algemene Kindergeneeskunde van het Sophia Kinderziekenhuis wil ik bedanken voor hun inzet en hulp bij het beoordelen van de kinderen die voor het Koortsonderzoek kwamen.

Margriet van Stuijvenberg, dank je wel voor de vlotte overname van deze onderzoekslijn. Ik wens je veel succes met de voortzetting.

Voorts zeg ik dank aan:

Mijn mede-onderzoekers op de benauwde, maar gezellige fellow-kamer (en daarbuiten) René Kornelisse, Marjon Cnossen, Hanneke IJsselstein, Arne van Teunenbroek, Anne de Vries, Yolanda den Ouden, Wouter de Waal, Hans van Goudoever, Eric Sulkers, Corine Koopman, Anneke Saarloos, Anneke Boerlage, Niels de Bruijn, Annemie Boehmer, Svatti Patandin en Theo Sas, voor hun collegialiteit en de goede onderlinge sfeer.

Jacqueline de Vogel en Riet Visser en Koos Lubbe voor hun behulpzaamheid bij de financiële zaken en hun belangstelling voor de voortgang van het onderzoek.

De CKB-leesclub, met onder andere David Bruijnvelds en Hauke Klomp, voor de leerzame en gezellige momenten.

Annemarie Harmsen, Jan Hendrik Richardus en Mingh Huang voor het nakijken van mijn Engels.

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Ook wil ik graag de volgende personen bedanken die niet zozeer hebben bij gedragen aan de inhoud van dit proefschrift, doch wier aanwezigheid in deze periode voor mij even belangrijk is geweest:

Mijn collega's en kamergenoten van het laatste jaar op het instituut Maatschappelijke Gezondheidszorg: René Eijkemans, Veerle Coupé, Pieta Krijnen, Kees van Bezooijen, Tineke Kurtz, Ilse Philips, Anton Kunst, Mariël Droomers, Wilco Graafmans, Karien

Stronks en Hans Bosma. Bedankt voor jullie ondersteuning en immer luisterend oor.

Alle medewerkers van het instituut voor Maatschappelijke Gezondheidszorg, voor hun hulp en gastvrijheid.

Prof. Dr J.P. Mackenbach, de projectleider van mijn huidige onderzoek, die mij nog de nodige tijd en gelegenheid gaf om dit proefschrift af te ronden.

De leden van de AZR/FGG-gebedsgroep, voor hun vriendschap en gebeden.

Mijn goede vrienden en kenissen die ik tijd tekort heb gedaan, met name in het laatste jaar, vanwege de drukte met dit boekje.

De gemeenteleden van de Maranathakerk in Vlaardingen, en in het bijzonder pastor Dr S.K. Thé, voor hun niet aflatende belangstelling, bemoediging en gebed. Ook wil ik de medewerkers in het kinder-, evangelisatie- en het vertalingsteam bedanken voor de extra geleverde inspanning toen ik 'het weer eens moest laten afweten'.

Natuurlijk zal ik nooit mijn ouders en mijn broers vergeten. Lieve papa en mama, ik wil jullie bedanken dat jullie voor mij die omgeving hebben weten te creëren, waarin ik mij heb kunnen ontwikkelen en waardoor ik kon gaan studeren, wat uiteindelijk heeft geleid tot dit proefschrift. Jan en Machiel, ook jullie wil ik bedanken voor jullie trouwe steun en hulp.

Boven alles dank ik God, die al deze mensen op mijn weg heeft geplaatst en mij de gelegenheid en kracht gaf om dit proefschrift te voltooien.

Curriculum vitae

Adrianus (Arjen) van Esch was born on October 14th, 1964, in Werkendam. He passed secondary school at the 'Gymnasium Camphusianum' in Gorinchem in 1983. In the same year, he started medical studies at the Erasmus University Medical School in Rotterdam. He obtained his medical degree in April 1991. After graduating, he was appointed as a researcher at the outpatient department of the Sophia Children's Hospital in Rotterdam, where he performed clinical research on the prediction, outcome, and prevention of recurrent febrile seizures. He was supervised by the pediatricians Drs G. Derksen-Lubsen and H.A. van Steensel-Moll. This project was conducted in collaboration with the Centre of Clinical Decision Sciences/Department of Public Health of the Erasmus University Rotterdam, headed by Prof.Dr Ir J.D.F. Habbema. In this period, the material for this thesis was collected. During the period October 1994 – April 1996, Arjen van Esch worked as a resident in pediatrics at the Sophia Children's Hospital in Rotterdam (head of department Prof.Dr H.K.A. Visser). At present he is a research fellow at the Department of Public Health of the Erasmus University Medical School in Rotterdam, where he conducts research on quality of care in stroke patients (supervisor Prof.Dr J.P. Mackenbach).

Appendix I

Letters and forms used in family history study

afdeling Polikliniek Algemene Kindergeneeskunde

datum 12 december 1991
:orkies nr.
's kenmerk ave
uw kenmerk
:nderwerp

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

sophia kinderziekenhuis
dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

Aan de ouders/verzorgers van
Vanessa

Geachte heer/mevrouw,

In 1988 heeft u met Vanessa het Sophia Kinderziekenhuis bezocht in verband met koortsstuipen.
Al enige tijd wordt op onze polikliniek wetenschappelijk onderzoek gedaan naar de oorzaak van terugkerende koortsstuipen.
Graag vragen wij uw medewerking voor dit onderzoek.

Dr. Van Esch zal u opbellen in de week van 16 december 1991. Als u meewerkt aan het onderzoek, zal hij u enkele vragen stellen.
De belangrijkste vragen zijn:

1. Heeft Vanessa na het laatste bezoek bij Dr. Offringa nog stuipen gehad?
   Hoe vaak en wanneer was dat?
2. Welke familieleden van Vanessa hebben ooit stuipen gehad?
   Hoe oud waren zij toen?

Het gesprek zal vijf tot tien minuten duren.
U hoeft niet zelf te bellen, ook hoeft u niet naar het ziekenhuis te komen.

Wij danken u bij voorbaat voor uw medewerking.

Met vriendelijke groeten,

A. van Esch, arts

M. Offringa, arts
Dr. G. Derksen-Lubsen, kinderarts

Sophia

afdeling Polikliniek Algemene Kindergeneeskunde

datum 13 januari 1992
doorkies nr.
ons kenmerk ave
uw kenmerk
onderwerp

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

sophia kinderziekenhuis
dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

Aan de ouders/verzorgers van
Vanessa

Geachte heer/mevrouw,

Het Sophia Kinderziekenhuis doet wetenschappelijk onderzoek om kinderen met koortsstuipen zo goed mogelijk te behandelen.
Vier weken geleden ontving u een brief over dit onderzoek. In deze brief vroegen wij of u ons wilde opbellen.
We vinden het jammer dat u toen niet heeft gereageerd.
Daarom vragen wij nu nog eens uw hulp bij dit onderzoek.

Graag zouden wij willen weten of Vanessa nog stuipen heeft gehad heeft en of andere familieleden ooit stuipen hebben gehad.
Wij kunnen u echter niet opbellen, omdat uw telefoonnummer onbekend is.
Het zou daarom fijn zijn als ú Dr. Van Esch wilt opbellen. Het nummer en de tijd staan in het vakje.

Telefoonnummer (0 10) - 4 63 61 96
op woensdag 20 november tussen 14.00 en 18.00 uur
óf op donderdag 21 november tussen 18.00 en 22.00 uur

Het gesprek zal 5 tot 10 minuten duren.
Wij danken u bij voorbaat voor uw medewerking.

Met vriendelijke groeten,

A. van Esch, arts

M. Offringa, arts
Dr. G. Derksen-Lubsen, kinderarts

P.S.: Eventueel kunt u ons ook bellen op (0 10) - 4 63 63 63.

Sophia

Koorts en Convulsie Follow Up Onderzoek

Patiënt **telefoon:** [ ]
naam / telefoon huisarts [ ]

Nr. [ ]

Naam kind [ ]
Geboortedatum (dd) [- -]
1e convulsie (dd) [- -]
Zeker koorts (T > 38.5 °C) bij 1e conv. ? 0 ja 0 nee
Ziekenhuis [ ]

Geslacht 0 man 0 vrouw

Risicofactoren (aanwezig rond 1e aanval)

1e graad familie-anamnese voor epilepsie 0 ja 0 nee
1e graad familie-anamnese voor koortsconv. 0 ja 0 nee
aantal keren koorts > 38.5 °C totaan 1e aanval [ ]
1e aanval: kenmerken.
Duur (actuele duur) [of > 15 min.] ..... minuten [0 ja 0 nee]
Multipele aanval 0 ja 0 nee
Partiële aanval/lateralisering 0 ja 0 nee
Blijvende neurologische afwijkingen 0 ja 0 nee [ ]
Temperatuur vóór 1e aanval (°C). [ ]
Temperatuur ná 1e aanval (°C) (op EHBO). [ ]
Recidief convulsie in eerste week 0 ja 0 nee
Nadere bijzonderheden eerste aanval: [ ]
Profylactische medicatie gestard: 0 ja 0 nee [zo ja, welke:]

Follow up Contact: datum (dd)	[- -]	[- -]	[- -]	[- -]
gesproken met (1 = ouder, 2 = H.A., 3 = ander)	[ ]	[ ]	[ ]	[ ]
betrouwbaarheid informatie (tekst)	[ ]	[ ]	[ ]	[ ]
onderzoeker	[ ]	[ ]	[ ]	[ ]
Koorts gehad				
aantal keren koorts >38.5 °C gehad	[ ]	[ ]	[ ]	[ ]
gebruik antipyretica	0 ja 0 nee	0 ja 0 nee	0 ja 0 nee	0 ja 0 nee
boven welke temperatuur (°C)	[ ]	[ ]	[ ]	[ ]
welk antipyreticum / toedieningsroute	[ ]	[ ]	[ ]	[ ]
gebruikte dosering (mg.)	[ ]	[ ]	[ ]	[ ]
actueel lichaamsgewicht (kg.)	[ ]	[ ]	[ ]	[ ]
toediening met welk tijds interval (uren)	[ ]	[ ]	[ ]	[ ]
Recidieven				
aantal convulsies in deze follow up periode (Indien > 0, op achterzijde doorgaan.)	[ ]	[ ]	[ ]	[ ]

Formulier voor afname van een gedetailleerde familie-anamnese

Naam: Datum 1e convulsie:	
1a. Landsaard biologische moeder: 1b. Landsaard biologische vader:	Ned? --> stamboom Idem
2a. Sibs (j/m, geb. datum) 2b. Sibs met koortsstuipen in anamnese (j/m, geb. datum) 2c. Sibs met epilepsie in anamnese (j/m, geb. datum)	
3a. Vader +/- familieleden met koortsstuipen in de anamnese (m/v, relatie tot proband, leeftijd) 3b. Vader +/- familieleden met epilepsie in de anamnese (m/v, relatie tot proband, leeftijd)	
4a. Moeder +/- familieleden met koortsstuipen in de anamnese (m/v, relatie tot proband, leeftijd) 4b. Moeder +/- familieleden met epilepsie in de anamnese (m/v, relatie tot proband, leeftijd)	
5. Aanvullend:	

Appendix II

Letters and forms used in genetic linkage study

afdeling Polikliniek Algemene Kindergeneeskunde

datum 30 maart 1993
doorkies nr.
ons kenmerk
uw kenmerk ave
onderwerp Genetisch onderzoek bij familiaire koortsstuipen

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

Aan de familieleden van Hermien

sophia kinderziekenhuis
dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

Geachte mijnheer/mevrouw,

Deze brief heeft u ontvangen van de ouders van Hermien. Wellicht hadden zij u al geïnformeerd over het genetisch onderzoek naar koortsstuipen in het Sophia Kinderziekenhuis. Dit onderzoek is van belang omdat de resultaten ervan de oorzaak van koortsstuipen kunnen opheldéren. Ook kan met de opgedane kennis de preventie en behandeling van koortsstuipen verbeterd worden.
Op dit moment zijn er nog maar enkele families genetisch onderzocht, en is er nog geen gen gevonden. Graag vragen wij u daarom, als eerste familie in Nederland, mee te werken aan het genetisch onderzoek naar koortsstuipen. Leest u het bijgaande informatie-formulier eens rustig door.
Als u meewerkt, wilt u dan het bijgaande toestemmings-formulier ingevuld in de bijgaande envelop retourneren? Dit formulier zal bij personen onder de achttien jaar ook door de ouders ondertekend moeten worden. Vervolgens wordt u uitgenodigd om naar het Sophia Kinderziekenhuis te komen voor bloedafname; eventueel kunnen wij bij u langs komen.
Bij vragen zijn wij graag bereid om u te woord te staan. U kunt ons bereiken via (0 10 - 4 63 63 63) in het Sophia Kinderziekenhuis.

Met vriendelijke groet,

A. van Esch, arts, mede namens

Dr. H.A. van Steensel-Moll, kinderarts
Prof. Dr. D. Lindhout, kinderarts, klinisch-geneticus

Sophia

Informatie Formulier voor de Familieleden

1. TITEL VAN HET ONDERZOEK: KOORTSSTUIPEN EN ERFELIJKHEID

2. DOEL EN BELANG VAN HET ONDERZOEK
Koortsstuipen komen bij 4% van alle kinderen voor. Ongeveer één op de drie kinderen krijgt opnieuw stuipen bij een volgende koortsperiode. Welke kinderen dat zijn is nu nog moeilijk te voorspellen. Het doel van dit onderzoek is om een mogelijk bestaande aanleg voor koortsstuipen te vinden. Als uiteindelijk een dergelijke aanleg wordt gevonden, zal de (kinder-) arts voortaan de kans op (herhalingen van) koortsstuipen nauwkeuriger kunnen vaststellen. Ook is dan duidelijker welke kinderen maatregelen ter voorkoming van koortsstuipen moeten krijgen, en voor welke kinderen dit niet nodig is.

3. UITVOERING
Alle familieleden vullen een vragenformulier over de medische voorgeschiedenis in. Dit wordt door de onderzoeksarts aangevuld met informatie uit medische dossiers. Afhankelijk van de verkregen informatie, zal de onderzoeksarts bloed van de verwanten afnemen. Het Instituut voor Klinische Genetica in Rotterdam zal vervolgens nagaan welk stuk DNA (dit is het erfelijk materiaal) de familieleden met koortsstuipen met elkaar gemeenschappelijk hebben.

4. DEELNAME
Indien u meedoet verzoeken wij u om uw personalia en enkele gegevens uit uw medische voorgeschiedenis in te vullen op het vragenformulier. Bloedafname vindt plaats, afhankelijk van uw medische voorgeschiedenis en (indien van toepassing) die van uw kinderen.

5. AANMELDING
Ons contact met u kan op verschillende manieren tot stand zijn gekomen. Het kan zijn dat wij uw adres en telefoonnummer via uw familie hebben verkregen. Ook kunt u zelf contact met ons opgenomen hebben. U kunt zich aanmelden door het toestemmingsformulier [1] te ondertekenen en terug te sturen. Hierop kunt u tevens uw adres en telefoonnummer invullen.
Na ontvangst van het formulier zullen wij contact met u opnemen en een afspraak met u maken voor de bloedafname.

6. UITSLAG/RESULTATEN
Als de uitslag van het onderzoek in algemene zin bekend is, zullen wij u daarover graag informeren. Het kan zijn dat we de komende jaren nog geen vorderingen zullen maken, die het mogelijk maken om met DNA onderzoek een diagnose te stellen of uit te sluiten. Als er echter wel een doorbraak komt, kan DNA onderzoek bij individuele personen wel een uitspraak mogelijk maken. Zonder uw uitdrukkelijke wens zullen wij u geen uitslag over uzelf geven. Wij zullen u uiteraard nooit een uitslag over anderen geven, alleen over uzelf.
Indien u een uitslag wenst te horen, kunt u zich ook door uw behandelend arts laten verwijzen voor erfelijkheidsadvies. De erfelijkheidsdeskundige kan dan de gegevens van ons onderzoek met uw toestemming opvragen en met u bespreken.
Indien bij dit DNA-onderzoek het gen voor koortsstuipen niet op chromosoom 20 blijkt te liggen, zal met behulp van het verkregen DNA naar de plaats van dit gen op een van de andere chromosomen worden gezocht. Hierbij wordt alleen onderzoek gedaan naar het gen voor stuipen.

7. RECHTEN
U bent altijd vrij om met het onderzoek te stoppen. Ook als u niet meedoet heeft u recht op erfelijkheidsadvies.
In het wetenschappelijk verslag zullen uw gegevens naamloos gemaakt worden.
Dit onderzoek is goedgekeurd door de Medisch Ethische Commissie van het Academisch Ziekenhuis van Rotterdam.

8. ONDERZOEKERS
Uw medewerking stellen wij zeer op prijs. Als u vragen of opmerkingen heeft dan kunt u zich wenden tot:

A. van Esch, arts, Sophia Kinderziekenhuis
Dr. H.A. van Steensel-Moll, kinderarts, Sophia Kinderziekenhuis
Prof. Dr. D. Lindhout, kinderarts-geneticus, Instit. Klinische Genetica R'dam

[1] Voor ondertekening zie het toestemmingsformulier (volgende pagina)

Toestemmingsformulier voor Familieleden ten bate van het Koppelingsonderzoek

Dit formulier betreft:

☐ Zichzelf: vul hieronder uw naam en geboortedatum in
☐ Zijn/haar zoon/dochter: vul hieronder zijn/haar naam en geboortedatum in

Naam: _____

Geboortedatum: _____

Adres: _____

Postcode en woonplaats: _____

Telefoonnummer: _____

1. Geeft u toestemming aan uw behandelende artsen dat zij u ons informatie geven over uw medische voorgeschiedenis?

   ☐ Ja
   ☐ Nee

2. Geeft u toestemming voor bloedafname ten bate van dit onderzoek?

   ☐ Ja
   ☐ Nee

3. Geeft u toestemming voor bloedafname ten bate van later onderzoek naar koortsstuipen op een van de andere chromosomen?

   ☐ Ja
   ☐ Nee

4. Wilt u te zijner tijd de uitslag van het onderzoek over u zelf weten?
   (Dit zal u na het bekend worden van de eventuele uitslag opnieuw gevraagd worden)

   ☐ Ja
   ☐ Nee
   ☐ Weet ik nog niet

Handtekening: _____

Handtekening ouder: _____
(indien het de gegevens betreft van uw kind onder de 18 jaar)

Invulformulier voor Familieleden

INSTRUCTIE

- Wilt u de vragen in de gegeven volgorde beantwoorden? Leest u elke vraag aandachtig door voordat u gaat antwoorden.

- Er zijn twee soorten vragen.
  Bij de meerkeuze-vragen kruist u het enige goede antwoord aan. Bijvoorbeeld vraag 5:

  Had u koorts?

  ☐ Ja
  ☐ Nee

  Bij de andere vragen geeft u een kort antwoord. Bijvoorbeeld vraag 8:

  Bent u toen door een huisarts onderzocht?

  ☐ Ja: Naam huisarts: *Van der Berg*

  Woonplaats huisarts: *Rotterdam*

  ☐ Nee

- De vragen van ALGEMENE GEGEVENS moeten door iedereen ingevuld worden. Ook de vragen van paragraaf I. IV. en V. van de MEDISCHE GEGEVENS moeten door iedereen ingevuld worden.
  Als u ooit een aanval heeft gehad, beantwoordt u de vragen van paragraaf II..
  Als u meerdere aanvallen heeft gehad beantwoordt u ook de vragen van paragraaf III.

- Graag met pen schrijven, niet met potlood of stift.

INHOUD

1. ALGEMENE GEGEVENS

2. MEDISCHE GEGEVENS

   Paragraaf I. Het optreden van aanvallen
   II. Vragen bij de eerste aanval
   III. Vragen bij de tweede en latere aanvallen
   IV. Medicijnen
   V. Hersenfilmpje (EEG)

ALGEMENE GEGEVENS

Uw personalia

Achternaam: _____

Meisjesnaam (indien van toepassing): _____

Voornamen: _____

Straat en huisnummer: _____

Postcode en woonplaats: _____

Telefoonnummer: _____

Geboortedatum: _____

Geboorteplaats: _____

Geslacht: _____

Personalia van uw vader

Achternaam: _____

Voornamen: _____

Geboortedatum: _____

Oorspronkelijke nationaliteit: _____

Personalia van uw moeder

Achternaam: _____

Meisjesnaam: _____

Voornamen: _____

Geboortedatum: _____

Oorspronkelijke nationaliteit: _____

Huisarts

Naam: _____

Adres: _____

Plaats: _____

Telefoonnummer: _____

Behandelend specialist (indien van toepassing)

Naam: _____

Naam ziekenhuis: _____

Plaats: _____

MEDISCHE GEGEVENS

I. Het optreden van aanvallen.

1. Heeft u ooit een plotselinge aanval van bewusteloosheid (niet bij flauwvallen) gehad?

   ☐ Ja
   ☐ Nee

Was uw antwoord op vraag 1. JA? Ga dan verder met vraag 2.
Was uw antwoord op vraag 1. NEE? Ga dan door met vraag 11.

II. Vragen bij de eerste aanval.

2. Op welke datum (welk jaar) vond de eerste aanval plaats?

   _____

3. Had u trekkingen van armen en benen?

   ☐ Ja
   ☐ Nee

4. Hoe lang duurde de aanval?

   ☐ Korter dan 1 minuut
   ☐ Tussen 1 en 15 minuten
   ☐ Langer dan 15 minuten
   ☐ Onbekend

5. Had u koorts bij deze aanval?

   ☐ Ja
   ☐ Nee

6. Is de temperatuur gemeten bij deze aanval?

   ☐ Ja, namelijk _____,_____°C
   ☐ Nee

7. Welke van de volgende oorzaken was aanwezig?

   ☐ Nekkramp of hersenvliesontsteking
   ☐ Hersenschudding of hoofdletsel
   ☐ Afwijkingen in het bloed
   ☐ Hersenbeschadiging
   ☐ Geen van bovengenoemde, namelijk: _____

8. Bent u toen door een huisarts onderzocht?

   ☐ Ja: Naam huisarts: _____

   Woonplaats huisarts: _____

   ☐ Nee

9. Bent u toen in het ziekenhuis onderzocht?

   ☐ Ja: Naam van het ziekenhuis: _____

   Plaats van het ziekenhuis: _____

   ☐ Nee

10. Welke diagnose is er voor deze aanval gesteld?

    ☐ Epilepsie
    ☐ Koortsstuip
    ☐ Anders, namelijk: _____

11. Heeft u, meer dan 24 uur later, nog een tweede aanval van bewusteloosheid (niet bij flauwvallen) meegemaakt?

    ☐ Ja
    ☐ Nee

Was uw antwoord op vraag 11. JA? Ga dan verder met vraag 12.
Was uw antwoord op vraag 1. NEE? Ga dan door met vraag 23.

III. Vragen bij de tweede aanval.

12. Op welke datum (welk jaar) vond de tweede aanval plaats?

    _____

13. Had u trekkingen van armen en benen?

    ☐ Ja
    ☐ Nee

14. Hoe lang duurde de aanval?

    ☐ Korter dan 1 minuut
    ☐ Tussen 1 en 15 minuten
    ☐ Langer dan 15 minuten
    ☐ Onbekend

15. Had u koorts bij deze aanval?

    ☐ Ja
    ☐ Nee

16. Is de temperatuur gemeten bij deze aanval?

    ☐ Ja, namelijk _____,_____°C
    ☐ Nee

17. Welke van de volgende oorzaken was aanwezig?

    ☐ Nekkramp of hersenvliesontsteking
    ☐ Hersenschudding of hoofdletsel
    ☐ Afwijkingen in het bloed
    ☐ Hersenbeschadiging
    ☐ Geen van bovengenoemde, namelijk: _____

18. Bent u toen door een huisarts onderzocht?

    ☐ Ja: Naam huisarts: _____

    Woonplaats huisarts: _____

    ☐ Nee

19. Bent u toen in het ziekenhuis onderzocht?

    ☐ Ja: Naam van het ziekenhuis: _____

    Plaats van het ziekenhuis: _____

    ☐ Nee

20. Welke diagnose is er voor deze aanval gesteld?

    ☐ Epilepsie
    ☐ Koortsstuip
    ☐ Anders, namelijk: _____

21. Heeft u, meer dan 24 uur na de tweede aanval, nog meer aanvallen van bewusteloosheid (niet bij flauwvallen) meegemaakt?

    ☐ Ja
    ☐ Nee

Vraag 22. hoeft u alleen in te vullen als uw antwoord op vraag 21. JA was.

22. Op welke leeftijd had u de laatste aanval?

    _____

IV. Medicijnen

23. Heeft u ooit medicijnen tegen epilepsie geslikt?

    ☐ Ja, namelijk: _____

    ☐ Nee

Was uw antwoord op vraag 23. JA? Ga dan verder met vraag 24.
Was uw antwoord op vraag 23. NEE? Ga dan door met vraag 28.

24. In welk jaar bent u met deze medicijnen begonnen?

    _____

25. In welk jaar bent u met deze medicijnen opgehouden?

    _____

26. Door welke specialist waren deze medicijnen voorgeschreven?

    _____

27. Wat was de naam en plaats van het ziekenhuis?

    _____

V. Hersenfilmpje (EEG)

28. Is er bij u ooit een hersenfilmpje (EEG) in het ziekenhuis gemaakt?

    ☐ Ja: Naam en plaats van het ziekenhuis: _____

    Datum(s): _____

    ☐ Nee

FAMILIE STAMBOOM

naam: _____
geb. dat: _____

grootouders

(uw vaders familie) (uw moeders familie)

tante tante oom oom vader moeder oom oom tante tante

UZELF broer broer zus zus

broers kind broers kind zus' kind zus'kind

broers kind broers kind zus' kind zus'kind

broers kind broers kind zus' kind zus'kind

Pas aan voor uw familie. Gebruik bijvoorbeeld extra strepen om tweede huwelijken of meer personen toe te voegen. Geef alstublieft tweelingen aan.
Geeft u voor elke persoon de achternaam (tenminste 3 eerste letters), meisjesnaam (i.v.t.), geboortedatum, leeftijd van overlijden (i.v.t.) en of de persoon wel ⊕ of geen ⊖ koortsstuipen heeft gehad.

Procedure dataverzameling koppelingsonderzoek

1. Contact met gezin van de proband
   - kennismaking met ouders van de proband
   - uitleg belang van het onderzoek
   - completeren stamboom (consanguiniteit, tweelingen, P-nummers)
   - info over algemene procedure
     . verspreiding informatie en formulieren onder familie
     . termijn voor retour toestemmingsformulier en adressen
     . familieleden voor venapunctie
   - praktisch: beschikbaarheid, vervoer, bereikbaarheid van familieleden voor venapunctie
   - verstrekken
     . 1 pakket per familielid
       * informatieformulier
       * toestemmingsformulier, adres en tel. in te vullen
     . 1 gefrankeerde retourenvelop per gezin

2. Contact met familieleden, na ontvangst toestemmingsformulier
   - schriftelijk
     . bedanken voor medewerking
     . uitnodigen voor venapunctie
     . afspraak voorstellen, gaarne contact indien ongelegen
   - bij geen respons familielid ouders proband benaderen voor reminder aan het betreffende familielid

3. Afname bloedmonsters
   - klinische genetica ingelicht over komst materiaal die dag
   - ontvangstruimte, koffie en gebak
   - ontvangst balie/receptie
   - individuele venapunctie
     . check identiteit/plaats op stamboom
     . check informed consent
     . vena punctie
       * volwassenen 4 vacutainers 7.5 ml, kinderen 2
       * naald + systeem
       * 2 stickers (ev. al ingevuld): # naam, voorletters
         # hr/mw, man/vrouw
         # P-nummer
       * formulier klinische genetica
       * kopie stamboom, betr. familielid aangekruist
       * buizen met stickers, formulier en stamboom (aan elkaar geniet)
       * formulier medische gegevens verstrekken, (thuis) laten invullen
       * gefrankeerde retourenvelop/afspraak maken om thuis te komen ophalen
       * buizen en formulieren naar laboratorium klinische genetica

4. Aanleggen genetische status/validatie verstrekte fenotypische gegevens
   - in genetische status gegevens van alle familieleden, met per familielid:
     . probandformulier
     . toestemmingsformulier
     . formulier medische gegevens
     . stamboom formulier, indien aangetrouwd familielid
   - ingevulde formulier met medische gegevens bespreken met betreffende familielid
   - gegevens cross-checken met nog levende oudere eerste graads verwanten
   - indien toestemming gegeven, gegevens huisarts opvragen
   - indien van toepassing, gegevens opvragen van betreffende specialist
   - gegevens huisarts/ziekenhuis invullen op medisch invulformulier
   - vergelijk gegevens familielid met gegevens huisarts/ziekenhuis
   - consensus bereiken over phenotypering (kinderarts en klin. geneticus)

5. Linkage analyse

Table Family Information

Relative	Direct information	Specialist	Fam.physician	Indirect information	Clinical classification
P01	FS (mother)	FS (peditrician)			affected
P02	FS (father)	FS (pediatrician)			affected
P04	FS (mother)	FS (pediatrician)			affected
P06	not available	not available	unknown	FS (daughter) no FS (husband) no FS (younger sib)	possibly affected
P10	FS (mother)	not available	unknown		affected
P15	FS (mother)	FS (specialist)			affected
P24	FS (mother)	not available	FS		affected
P25	unknown (P06)	not available	unknown	FS (niece) no FS (husband) unknown (brother in law)	possibly affected
P27	during measles (P33)	record P02		FS (P07)	affected
P29	FS (mother)	not available	not available		affected
P36	not available	not available	not available	FS 2 brothers in law (P26 and P07)	possibly affected
P38	FS (father)	not available	not available	FS (sister)	affected
P39	FS (older brother)	not available	not available		possibly affected
All others	no FS	no FS	no FS	no FS	unaffected

afdeling Polikliniek Algemene Kindergeneeskunde

datum 18 oktober 1996
doorkies nr.
ons kenmerk AvE
uw kenmerk
onderwerp Linkage analyse bij familiaire febriele convulsies

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

sophia kinderziekenhuis
dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

Aan de familie van Hermien

Geachte Mijnheer, Mevrouw (en kinderen),

Graag informeren wij u over de uitkomst van ons onderzoek naar de erfelijkheid van koortsstuipen. U en bijna 30 andere familieleden hebben indertijd met veel inzet meegewerkt aan dit onderzoek en uw bloed laten onderzoeken. Het is nu wetenschappelijk bewezen, dat het gen voor Benigne Familiaire Neonatale Convulsies (BFNC) niet in uw familie voorkomt. Koortsstuipen in uw familie worden dus niet door dit BFNC-gen veroorzaakt. Daarmee is dit deel van het onderzoek afgesloten. U heeft hiermee een belangrijke bijdrage geleverd aan het erfelijk onderzoek naar koortsstuipen. Wij zullen de resultaten hiervan in een wetenschappelijk artikel vastleggen en ter publicatie voorleggen aan een internationaal medisch tijdschrift.
Wij willen u hartelijk danken voor de enthousiaste medewerking die u verleend heeft aan dit onderzoek.

Helaas konden wij u nu pas berichten over de uitkomst van het onderzoek, doordat er in het laboratorium een aantal nieuwe analyses gedaan moesten worden. Ook bleek de opbouw van de familie aanzienlijke technische problemen te leveren bij de computer analyse. Het duurde enige tijd voordat we hiervoor een beschikbare deskundige analist gevonden hadden.

Het is zeer waarschijnlijk dat er een erfelijke aanleg voor koorststuipen bestaat. Daarom zal vervolg onderzoek worden uitgevoerd, om de oorzaak van koortsstuipen beter te kunnen begrijpen. In dit nieuwe onderzoeksproject zullen gezinnen met twee broertjes of zusjes met koortsstuipen onderzocht worden met behulp van een nieuwe onderzoeksmethode. Over drie jaar hopen wij hiervan resultaten te hebben. Indien u prijs stelt op informatie over de uitkomst van dit vervolg onderzoek, kunt u de bijgaande antwoordstrook invullen en opsturen naar mw. Dr. M. van Stuijvenberg.

Met vriendelijke groeten,

A. van Esch, arts

M. van Stuijvenberg, arts
Dr. H.A. van Steensel-Moll, kinderarts

Sophia

Appendix III

Letters and forms used in trial of ibuprofen and acetaminophen

afdeling Polikliniek Algemene Kindergeneeskunde

datum 1 mei 1992
doorkies nr.
ons kenmerk ave
uw kenmerk
onderwerp

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

sophia kinderziekenhuis

dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

De ouders/verzorgers van
Pascal

Geachte ouders/verzorgers van Pascal,

Graag vragen wij uw medewerking voor het Koortsonderzoek, dat voor uw kind van belang is. Omdat uw kind koortsstuipen heeft gehad, is het belangrijk om te voorkomen dat het hoge koorts krijgt. Daarom vragen wij uw medewerking voor dit onderzoek.

In het Koortsonderzoek wordt de werking van twee medicijnen onderzocht bij kinderen die koortsstuipen hebben gehad. Deze medicijnen zijn ibuprofen- en paracetamol-drank.
In de bijgaande folder vindt u uitgebreide informatie over het onderzoek. Leest u die op uw gemak door. Ook het toestemmingsformulier is bijgevoegd. Hierop kunt u uw medewerking schriftelijk vastleggen als u met uw kind naar het ziekenhuis bent gekomen.
Bij vragen kunt u mij bellen op **(010) - 4 63 60 61.**

Als uw kind overdag méér dan 38.4 °C koorts krijgt, kunt u ons laten oproepen op **(010) - 4 63 60 61.** Zeg daarbij dat u voor het Koortsonderzoek belt. Wij zullen u direct terugbellen.

Met vriendelijke groet,

A. van Esch, arts

Dr. G. Derksen-Lubsen, kinderarts

Sophia

TOESTEMMINGS-FORMULIER KOORTSONDERZOEK

Aan de ouder(s)/ verzorger(s) van: _____

1. INLEIDING
   Jonge kinderen maken vaak een koortsperiode door. 5% van hen reageert daarop met koortsstuipen. Deze kunnen enkele minuten tot een uur duren. 30% tot 50% van de kinderen krijgt opnieuw koortsstuipen bij een volgende koortsperiode.

2. REDEN VAN HET ONDERZOEK
   Omdat het bij deze kinderen belangrijk is om te voorkomen dat ze hoge koorts krijgen, onderzoeken we de koortsverlagende werking van paracetamol en ibuprofen. Deze middelen worden al jaren gebruikt bij de behandeling van koorts, ontstekingen en verschillende soorten pijn. Het is echter onbekend of zij de koorts bij deze kinderen voldoende verlagen en hoe lang zij de koorts verlagen.

3. OPZET VAN HET ONDERZOEK
   Als u thuis bij uw kind 38,5 °C of meer koorts meet, neemt u contact met de onderzoekers op en komt u met uw kind naar de EHBO van het Sophia Kinderziekenhuis. Als na lichamelijk onderzoek geen verdere behandeling nodig is, krijgt u ibuprofen siroop of paracetamol siroop mee. U weet niet welk van de twee middelen uw kind krijgt. Thuis geeft u uw kind vier keer per dag de siroop, gedurende twee of drie dagen. De eerste dag meet u op vijf tijdstippen de temperatuur en schrijft die op in het patiëntenboekje. Na twee of drie dagen bezoekt u onze polikliniek opnieuw en geeft u het ingevulde boekje terug.

4. BIJWERKINGEN
   Bijwerkingen komen zeer zelden voor na inname van paracetamol en ibuprofen. Deze kunnen eventueel buikpijn, misselijkheid, braken of diarree zijn.

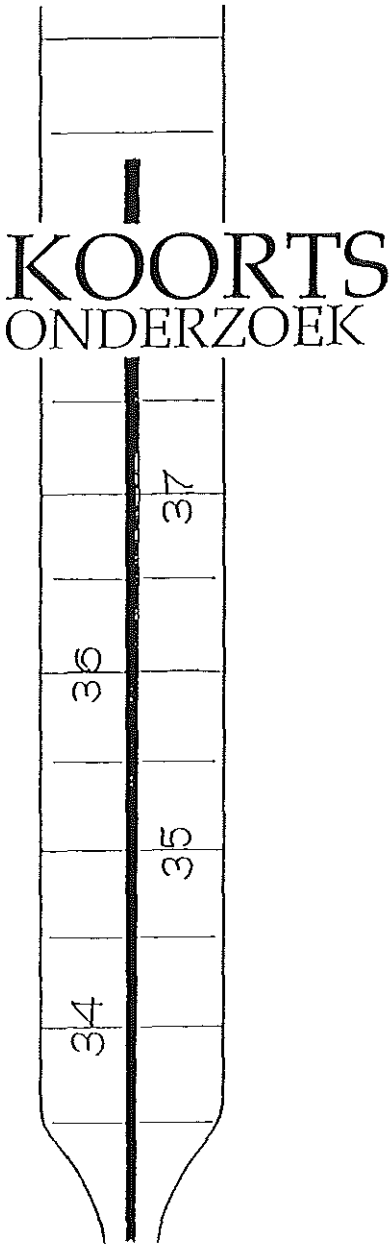
5. DEELNAME
   U bent vanzelfsprekend altijd vrij om met het onderzoek te stoppen. Uw toestemming kunt u hieronder schriftelijk vastleggen.
   Dit onderzoek is goedgekeurd door de Medisch Ethische Commissie van het Academisch Ziekenhuis van Rotterdam.

6. DE ONDERZOEKERS
   Uw medewerking stellen wij zeer op prijs. Mocht u in de loop van het onderzoek aanvullende vragen hebben dan kunt u zich wenden tot:

A. van Esch, arts
Dr. G. Derksen-Lubsen, kinderarts
M. Offringa, arts

Bij akkoord,
handtekening ouder(s)/verzorger(s): _____

Na ondertekening gaarne opsturen in bijgaande envelop.


KOORTS
ONDERZOEK
37
36
35
34

Het Koortsonderzoek, waarom?

Dit is een onderzoek naar de behandeling van koorts bij kinderen die koortsstuipen hebben gehad. Het is bij deze kinderen belangrijk om te voorkomen dat ze hoge koorts krijgen. Daarom bestuderen we de werking van twee koortsverlagende medicijnen, ibuprofen en paracetamol. Deze middelen worden al jaren gebruikt bij de behandeling van koorts, ontstekingen en pijn. Het is echter onbekend of zij koorts bij kinderen voldoende verlagen en hoe lang zij de koorts verlagen. Om dit goed te kunnen onderzoeken is de medewerking van veel ouders nodig. Daarom willen we graag dat ook ú meedoet aan het Koortsonderzoek

Wat houdt het onderzoek in?

Als u aan het Koortsonderzoek wilt meedoen, meet u bij koorts de temperatuur van uw kind. Als de temperatuur hoger dan 38,4 °C is, wordt uw kind in het ziekenhuis onderzocht. Er mogen dan echter nog géén koortsverlagende middelen of antibiotica gegeven zijn.
Wanneer uw kind in aanmerking komt voor het onderzoek, krijgt u een digitale Philips thermometer en siroop mee naar huis. In de siroop zit ibuprofen of paracetamol. U weet niet welk medicijn uw kind krijgt. Gedurende twee tot drie dagen geeft u het medicijn. Bovendien meet u de eerste dag op vijf tijdstippen de temperatuur en noteert die op een lijst. Op de dag na uw bezoek aan het ziekenhuis zullen wij u opbellen om te vragen hoe het gaat. Na twee tot drie dagen wordt uw kind weer onderzocht op de polikliniek. U levert de ingevulde temperatuurlijst en de medicijnen in.

Bij de volgende koortsperiode van uw kind belt u opnieuw naar het ziekenhuis voor het Koortsonderzoek. U doet dan voor de tweede keer mee met het onderzoek. Het onderzoek verloopt hetzelfde als de eerste keer. U meet de temperatuur met de thermometer die u de eerste keer heeft meegekregen. U krijgt nieuwe siroop mee.

Wat zijn de bijwerkingen?

Bijwerkingen komen zeer zelden voor na inname van paracetamol en ibuprofen. Deze kunnen eventueel buikpijn, misselijkheid, braken of diarree zijn.

Wat te doen als u meewerkt?

Op werkdagen én in het weekend kunt u zich 24 uur per dag aanmelden voor het onderzoek. U belt **(010) - 4 63 63 63** als uw kind boven 38,4 °C koorts krijgt. U krijgt dan de telefonist(e) van het ziekenhuis aan de lijn. Tegen hem/haar zegt u dat u belt voor het Koortsonderzoek van Dr. Van Esch. Ook geeft u uw telefoonnummer door.
Vervolgens wordt u snel door één van de onderzoek-artsen teruggebeld. Hij zal nagaan of uw kind mee kan doen aan het onderzoek. Uw kind kan alleen meedoen als het nog géén antibiotica of koortsverlagende middelen heeft gekregen. Als dat zo is, wordt u gevraagd om met uw kind naar de EHBO van het Sophia Kinderziekenhuis te komen.

Op de EHBO zal de arts uw kind nakijken, om vast te stellen wat de oorzaak is van de koorts. Als verder onderzoek of behandeling nodig is, dan zal die volgens de normale gang van zaken plaatsvinden.

De volgende keer dat uw kind weer koorts boven 38,4 °C krijgt, doet u op dezelfde manier aan het onderzoek mee als de eerste keer.

De aanmelding in het kort

1. Wanneer u denkt dat uw kind koorts heeft, meet u snel de rectale temperatuur.

2. Als u méér dan 38,4 °C koorts meet, belt u **(010) - 4 63 63 63.**

3. Daarna wordt u door één van de onderzoek-artsen teruggebeld. Hij zal u zeggen of uw kind mee kan doen aan het onderzoek.

Als u nog vragen heeft...

Als u vragen heeft over het Koortsonderzoek of over de behandeling met ibuprofen of paracetamol kunt u telefonisch bij ons terecht.

Tenslotte

Als u dat wilt, kunt u altijd stoppen met uw deelname aan het Koortsonderzoek.
Wij danken u bij voorbaat voor uw medewerking.

afdeling Polikliniek Algemene Kindergeneeskunde

datum 29 april 1992
doorkies nr.
ons kenmerk ave
uw kenmerk
onderwerp

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

sophia kinderziekenhuis
dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

De Weledelgeleerde Heer
H. Uisarts
Postlaan 1
1111 AA Koortsendam

Geachte collega,

Uw patiënt Pascal, geboren 1.1.91 en wonende Tempweg 39 te Koortsendam, heeft op 1 april 1992 het Sophia Kinderziekenhuis bezocht in verband met een koortsconvulsie.
Momenteel doen wij onderzoek naar het effect van paracetamol- en ibuprofen-siroop op het beloop van de koorts bij kinderen met een koortsconvulsie in de anamnese. De ouders van uw patiënt verlenen medewerking aan dit onderzoek. Uw patiënt zal bij de volgende twee koortsperioden met ibuprofen of paracetamol behandeld worden, als aan de insluitingscriteria van het onderzoek is voldaan (overdag koorts boven 38.4 °C, geen gebruik van antibiotica of antipyretica).

De gang van zaken is als volgt:
Als Pascal overdag meer dan 38.4 °C koorts krijgt, zullen de ouders direct telefonisch contact met ons opnemen. Als geschiktheid voor het onderzoek waarschijnlijk is, komen zij met hun kind naar de EHBO van het Sophia Kinderziekenhuis. Het kind wordt daar beoordeeld; zo nodig zal aanvullend onderzoek en behandeling plaatsvinden.
Als aan alle criteria van het onderzoek is voldaan, zal uw patiënt thuis gedurende drie dagen paracetamol of ibuprofen siroop krijgen. Tevens meten de ouders de eerste dag op vijf tijdstippen de temperatuur. Zij kunnen gedurende deze periode 24 uur per dag contact met ons opnemen. Zo nodig vindt een herbeoordeling op de polikliniek plaats. Na drie dagen leveren de ouders de temperatuurlijst in. Het kind wordt opnieuw beoordeeld. Mocht verder onderzoek of behandeling geïndiceerd zijn, dan zullen wij daar voor zorgen.
Bij de volgende koortsperiode zal het onderzoek volgens de zelfde procedure verlopen.

De ouders kunnen hun kind door de week én in het weekend aanmelden, op elk uur van de dag.
Na afloop van de behandeling zult u bericht van ons krijgen.
Wij hopen dat u kunt instemmen met de gevolgde procedure.
Voor uw vragen zijn wij te bereiken op het bovenvermelde telefoonnummer.

Met collegiale hoogachting,

Drs. A. van Esch, arts, trialcoördinator
Mw. dr. G. Derksen-Lubsen, kinderarts

Bijlagen: 1. Samenvatting protocol
2. Ouderfolder

KOORTSONDERZOEK op de Polikliniek Algemene Kindergeneeskunde

SAMENVATTING PROTOCOL

DOEL

Vergelijking van intensiteit en duur van de koortsdaling bij ibuprofen- en paracetamol-medicatie (volgens de onderstaande dosering) bij de behandeling van koorts bij kinderen die een koortsconvulsie hebben doorgemaakt.

PATIËNTEN

Kinderen van één tot drie jaar oud, die het Sophia Kinderziekenhuis wegens een koortsconvulsie hebben bezocht. De ouders worden schriftelijk en mondeling over de studie geïnformeerd, waarna zij het informed consent formulier kunnen ondertekenen.
De kinderen komen in aanmerking voor het Koortsonderzoek indien zij meer dan 38,4 °C koorts krijgen.
Een kind kan meerdere malen aan de studie deelnemen.
Kinderen die antibiotica krijgen, worden uitgesloten.

INTAKE PROCEDURE

Bij meer dan 38.4 °C koorts bellen de ouders de portier, die hun naam en telefoonnummer noteert. Vervolgens zet hij de semafoon van de onderzoeker aan.
De onderzoeker neemt contact op met de ouders en gaat na of voldaan wordt aan de inclusie-criteria. Dan vraagt hij de ouders om met hun kind direct naar de EHBO te komen. De onderzoeker geeft hun komst door aan de verpleging van de EHBO en hij is zelf binnen een half uur aanwezig.
De onderzoeker neemt de anamnese af en doet algemeen lichamelijk onderzoek. Hij wordt door de kinderarts gesuperviseerd.
De ouders kunnen hun kind door de week én in het weekend tussen 7.30 en 18.00 uur aanmelden. Buiten deze uren vindt er geen intake van patiënten plaats.

MEDICATIE EN OBSERVATIE

De kinderen krijgen dubbelblind gerandomiseerd 4 maal daags ibuprofen siroop 20 mg/ml,
5 mg/kilogram per dosis óf paracetamol siroop 40 mg/ml, 10 mg/kilogram per dosis.
De toediening van de eerste dosis en de eerste meting van de rectale temperatuur vinden op de polikliniek plaats. Thuis dienen de ouders gedurende twee of drie dagen de studie-medicatie toe. Tevens meten zij 2, 4, 6, 12 en 24 uur na de eerste dosis de rectale temperatuur met een door ons verstrekte digitale thermometer. Zij noteren de temperatuur op een standaard formulier. Gedurende de studieperiode is de onderzoeker telefonisch bereikbaar. Na 48 tot 72 uur vindt een tweede bezoek aan de polikliniek plaats. Indien noodzakelijk wordt een afspraak voor een eerder bezoek gemaakt.

ANALYSE

In totaal zullen er 100 koortsperioden in de studie worden opgenomen.
De temperatuurverschillen tussen de koortsperioden die zijn behandeld met ibuprofen en paracetamol zullen worden vergeleken op verschillende tijdstippen.

A. van Esch, trial-coördinator
20 februari 1992

PATIËNTEN-BOEKJE KOORTSONDERZOEK

Datum:	: ..../..../199..
Naam patiënt	:
	.....
	.....
Nummer patiënt	: ....
Nummer koortsperiode (1/2)	: ..
Gewicht (kg)	: .... kg
Dosis (0.25ml/kg afgerond op 0.2 ml)	: .... ml

Wijze van toediening:

De fles voor gebruik schudden.
De spuit op de dop van de fles zetten. Het geheel ondersteboven houden.
Dan de zuiger naar beneden trekken tot het maatstreepje van .... ml.
De spuit leegdrukken op een grote eetlepel en de drank laten innemen.

Bedankt voor uw medewerking.

Handtekening ouder(s) : .....

MEDICATIE

tijd (in uren)		In te vullen door arts: tijdstip (uren + minuten)	datum	hoeveelheid (ml)	In te vullen door ouders/verzorgers: tijdstip waarop gegeven	gegeven hoeveelheid	opmerkingen
dag 1	0						
	6						
	12						
	18						
dag 2	0						
	6						
	12						
	18						
dag 3	0						
	6						
	12						
	18						

TEMPERATUUR

tijd (in uren)		In te vullen door arts: tijdstip (uren + minuten)	datum	In te vullen door ouders/verzorgers: tijdstip waarop gemeten	temperatuur	opmerkingen
dag 1	0					
	2					
	4					
	6					
	12					
	24					

AFSPRAAK bij : .....

DAG, DATUM en TIJD : .....

TELEFOON : (0 10) - 4 63 63 63

SOPHIA KINDERZIEKENHUIS
Boots Pharmaceuticals

KOORTSONDERZOEK STUDIE BR 1178
Koortsconvulsie

Initialen patient:

Datum: | | | | | | | |

Patientnummer: 092
Koortsperiode: 2

TOELATINGSCRITERIA

GESCHIKT ALS DEZE HOKJES ZIJN AANGEKRUIST

Leeftijd tussen 1 en 4 jaar	JA	NEE
Poliklinische patient	JA	NEE
Overigens gezond kind	JA	NEE
Koortsconvulsie na 31 mei 1991	JA	NEE
Optreden van de koorts tussen 7.30 en 18.00 uur	JA	NEE
Thuis rectale temperatuur ≥ 38.5 graden Celsius	JA	NEE
Laatste 48 uur antipyretica gehad	JA	NEE
Laatste 48 uur systemische antibiotica gehad	JA	NEE
Indicatie voor systemische antibiotica op dit moment	JA	NEE
Contra-indicatie voor antipyretica	JA	NEE
Ondertekende toestemming	JA	NEE

START

ALGEMENE ANAMNESE

Koorts ≥ 38.5 °C sinds:

datum: | | | | | | |

tijd: | | | | hoogte koorts: | | °C

Geboortedatum: | | | | | | | |

Geslacht: M V

Medicijngebruik: ..... NEE JA nl.: .....

Recent contact met infectie-bron: ..... NEE JA nl.: .....

Handtekening onderzoeker:

→ **Ga door met pagina 2.**

SOPHIA KINDERZIEKENHUIS
Boots Pharmaceuticals

KOORTSONDERZOEK STUDIE BR 1178
Koortsconvulsie

Initialen patient:

Datum: | | | | | | |

Patientnummer: 092
Koortsperiode: 2

SPECIËLE ANAMNESE
Klachten over:

* ogen.....	NEE	JA	→ nl.: .....
* oren.....	NEE	JA	→ nl.: .....
* neus/keel.....	NEE	JA	→ nl.: .....
* resp. systeem.....	NEE	JA	→ nl.: .....
* circ. systeem.....	NEE	JA	→ nl.: .....
* spijsvert. systeem....	NEE	JA	→ nl.: .....
* urogen. systeem.....	NEE	JA	→ nl.: .....
* endocr. systeem.....	NEE	JA	→ nl.: .....
* huid.....	NEE	JA	→ nl.: .....
* bew. apparaat.....	NEE	JA	→ nl.: .....
* centr. zenuwst.....	NEE	JA	→ nl.: .....

SPECIFICEER KLACHT:

LICHAMELIJK ONDERZOEK
Vitale kenmerken

Temperatuur (rectaal).... [ ] °C Pols: ..... [ ] /min.

Gewicht: ..... [ ] kg. Ademhaling: ..... [ ] /min.

Observatie score (zie toelichtingsblad, pagina 7)
0 = normaal; **1** = matig ziek/gestoord; **2** = ernstig ziek/gestoord

Eerste algemene indruk: ...	[0] [1] [2]	Grijpt en speelt:	[0] [1] [2]
Kleur:	[0] [1] [2]	Maakt contact:	[0] [1] [2]
Hydratie:	[0] [1] [2]	Stemming:	[0] [1] [2]
Ademhaling:	[0] [1] [2]	Bewegingen:	[0] [1] [2]
Bewustzijn:	[0] [1] [2]		

Handtekening onderzoeker:

→ Ga door met pagina 3.

SOPHIA KINDERZIEKENHUIS
Boots Pharmaceuticals

KOORTSONDERZOEK STUDIE BR 1178
Koortsconvulsie

Initialen patient:

Datum: | | | | | | |

Patientnummer: 092
Koortsperiode: 2

LICHAMELIJK ONDERZOEK
Afwijkingen op het gebied van:

			SPECIFICEER AFWIJKING:
* meningeale prikkeling.....	NEE	JA	nl.: .....
* huid.....	NEE	JA	nl.: .....
* slijmvliezen.....	NEE	JA	nl.: .....
* lymfeklieren.....	NEE	JA	nl.: .....
* oren.....	NEE	JA	nl.: .....
* mond, neus, keel.....	NEE	JA	nl.: .....
* hals.....	NEE	JA	nl.: .....
* thorax.....	NEE	JA	nl.: .....
* buik.....	NEE	JA	nl.: .....
* overig.....	NEE	JA	nl.: .....

SAMENVATTING
Anamnese en lichamelijk onderzoek: .....
.....
.....
.....
Laboratoriumonderzoek: .....
.....
.....
.....
Diagnose c.q. werkhypothese: .....
Studiemedicatie: 4 dd..... ml.
Andere therapieën: .....
.....
.....

Tijd: | | | |

Onderzoeker:

.....
Handtekening:

.....

CHECKLIST
Ingevuld:
* Onderzoeksformulieren..... ☐
* Hoeveelheid suspensie op label ☐
Uitleg:
* Medicatie toediening..... ☐
* Welke arts is te bereiken..... ☐
* Invullen patientenboekje..... ☐

MEEGEVEN
1. Trial medicatie en spuit (Let op nummers)..... ☐
2. Patientenboekje..... ☐
3. Thermometer..... ☐
4. Controle-afspraak bij Dr..... (over 2 of 3 dagen)..... ☐

SOPHIA KINDERZIEKENHUIS
Boots Pharmaceuticals

KOORTSONDERZOEK STUDIE BR 1178
Koortsconvulsie

CONTROLE - BEZOEK

Initialen patient:

Datum: | | | | | | |

Patientnummer: 092
Koortsperiode: 2

LICHAMELIJK ONDERZOEK
Vitale kenmerken

Temperatuur (rectaal)..... °C Pols: ..... /min.

Gewicht: ..... kg. Ademhaling: ..... /min.

Observatie score (zie toelichtingsblad, pagina 7)
0 = normaal; 1 = matig ziek/gestoord; 2 = ernstig ziek/gestoord

Eerste algemene indruk: ... [0] [1] [2]
Kleur: ..... [0] [1] [2]
Hydratie: ..... [0] [1] [2]
Ademhaling: ..... [0] [1] [2]
Bewustzijn: ..... [0] [1] [2]
Grijpt en speelt: .... [0] [1] [2]
Maakt contact: ..... [0] [1] [2]
Stemming: ..... [0] [1] [2]
Bewegingen: ..... [0] [1] [2]

CONVULSIE
Heeft het kind een convulsie gehad?
JA NEE

Tijd: | | |
Datum: | | | | | |
Duur aanval > 15 min.?
JA NEE
Meerdere aanvallen?
JA NEE
Partiële aanval / lateralisering?
JA NEE

TERUGTREKKING UIT DE STUDIE
Is de medicatie-toediening binnen 48 uur gestaakt?
NEE JA → Tijd: | | | | Datum: | | | | | | |

Zijn er systemische antibiotica toegediend? → S.v.p. pagina 5 invullen
NEE JA → Tijd: | | | | Datum: | | | | | | |

ONGEWENSTE GEBEURTENISSEN / BIJWERKINGEN
Is er sprake geweest van ongewenste gebeurtenissen c.q. bijwerkingen?
NEE JA → S.v.p. pagina 6 invullen

Tijd: | | | | |

Onderzoeker:

.....

Handtekening:

.....

CHECKLIST
* Van toepassing zijnde onderzoeks-formululieren ingevuld..... ☐
* Patientenboekje ontvangen..... ☐
* Overgebleven medicatie teruggenomen.... ☐
* Instructies voor eventuele nieuwe koortsperiode gegeven..... ☐

SOPHIA KINDERZIEKENHUIS
Boots Pharmaceuticals

KOORTSONDERZOEK STUDIE BR 1178
Koortsconvulsie

ADDITIONAL DATA AND WITHDRAWAL

Child's initials:

Date:

Patientnummer: 092
Koortsperiode: 2

Date treatment ceased | Day | Mo | Yr |

Who stopped the treatment?

Please tick one box

The parent / guardian	
The investigator	
Jointly	
Another (specify below)	

Reason for withdrawal:

Please tick one box

Complete recovery	
Lack of response	
Adverse events (Please complete page 6)	
Lost to follow-up	
Systemic antibiotics indicated	
Other (specify below)	

Any additional information:

Investigator:.....

Signature.....

→ Ga door met pagina 4.

SOPHIA KINDERZIEKENHUIS
Boots Pharmaceuticals

KOORTSONDERZOEK STUDIE BR 1178
Koortsconvulsie

ADVERSE EVENTS RECORD

Child's initials:
Age: | Sex: | Weight:

Date: | | | | | | |

Patientnummer: 092
Koortsperiode: 2

Nature of Adverse Event	Any serious Adverse Event must be reported to the study director within one working day. Please arrange for follow-up of all such events.
Report type	Initial ☐ Follow Up ☐ Final ☐
Type of event	Single episode ☐ Recurrent ☐ Continuous ☐
Type of onset	Gradual ☐ Sudden ☐ Unknown ☐
Date and time of onset	| | | | | | Day Month Year (24 hour clock) | | | |
Date and time stopped (if applicable)	| | | | | | Day Month Year (24 hour clock) | | | |
Severity	Mild ☐ Moderate ☐ Severe ☐
Action taken	None ☐ Study treatment reduced ☐ Discontinued study treatment * ☐ *If therapy permanently discontinued complete withdrawal form. Symptomatic therapy ☐ Subject hospitalised ☐ Other ☐ Specify.....
Relation to study drug	Definite ☐ Possible ☐ None ☐ Probable ☐ Doubtful ☐ Unknown ☐
Outcome	Ongoing ☐ Recovered ☐ * If death occurs complete withdrawal form. Alive with sequelae ☐ Death* ☐

Has the patient experienced a similar adverse event before?

YES ☐ Please give details below NO ☐

Additional information:

Investigator: ..... Signature: .....

→ Ga door met pagina 4.

afdeling Polikliniek Algemene Kindergeneeskunde

datum 11 december 1992
doorkies nr.
ons kenmerk ave
uw kenmerk
onderwerp Koortsonderzoek

het sophia kinderziekenhuis
vormt samen met het ziekenhuis dijkzigt het
academisch ziekenhuis rotterdam

sophia kinderziekenhuis

dr. molewaterplein 60
3015 GJ rotterdam
telefoon 010-463 63 63

De ouders/verzorgers van
Pascal

Geachte ouders/verzorgers van Pascal,

U heeft uw medewerking toegezegd voor het Koortsonderzoek.
In dit onderzoek bekijken we of ibuprofen en paracetamol hoge koorts kunnen voorkomen bij kinderen die koortsstuipen hebben gehad.
Op dit moment hebben 18 kinderen meegedaan aan het onderzoek. Al deze kinderen hebben tijdens medicijngebruik geen koortsstuipen en geen bijwerkingen gehad.

Wij horen graag hoe het met Pascal gaat en of Pascal wel eens koorts heeft gehad, maar u niet in de gelegenheid was om naar het ziekenhuis te komen.
Daarom willen wij u vragen om op woensdag 13 januari a.s. tussen 9.00 en 12.00 uur telefonisch contact met ons op te nemen via (0 10) - 4 63 61 96.
Wij wensen u het allerbeste toe in 1993.

Met vriendelijke groet,

A. van Esch, arts

Dr. H.A. van Steensel-Moll, kinderarts
M. Offringa, arts

Sophia

FORMULIER FOLLOW-UP KOORTS EN RECIDIEF CONVULSIES TIJDENS TRIAL

A. Tijd: ..... Naam: ..... Geb. datum: .....

Datum laatste contact SKZ: .....

Toestemming gegeven: ja/nee

B. Sindsdien (ziek geweest met) koorts: Ja ---> B. / Nee ---> C.

Aantal keren:	.....			
Data/periode:	.....	.....	.....	.....
Gemeten:	ja/nee	ja/nee	ja/nee	ja/nee
Hoogte:	.....	.....	.....	.....
Boven 38.4 C:	ja/nee	ja/nee	ja/nee	ja/nee
SKZ gebeld:	ja/nee	ja/nee	ja/nee	ja/nee
Nee; reden:	....	....	....	....
Ja; naam arts:	.....	.....	.....	.....
Datum/tijd:	.....	.....	.....	.....
Contact huisarts:	ja/nee	ja/nee	ja/nee	ja/nee

C. 1. Nog ergens vragen over?

2. Als ..... overdag koorts, gelijk bellen; bij vragen altijd bellen.

3. Bedankt voor het bellen.

Appendix IV

Tables of studies of ibuprofen and acetaminophen

Table 1 -- Pharmacokinetics of Ibuprofen and Acetaminophen in children

Author, year (number)	Drug+dose (mg/kg)	C_{max} µg/l	T_{cmax} (hrs)	$T_{cmax} - T_{\Delta Tempmax}$ (hrs)	$T_{1/2}$ (hrs)	Remarks
Kauffman, 1992 n=49	Ibu 8	35	0.7	1–3	1.6	Antibiotics used
Brown, 1992 n=153	Ibu 5	20	1–1.5	2.5	1.7	Age and Temp0
	Ibu 10	40		2.5	1.5	influence
	Ace 12.5	20	0.5–1	2.5	1.9	ΔTempmax
Wilson, 1982 n=38	Ace 9		0.7	1.9	1.7	
	Ace 12		0.6	2.3	1.7	
Nahata, 1992 n=56	Ibu 5	28				
	Ibu 10	43				
Walson, 1989 n=127	Ibu 5	24				
	Ibu 10	40				
	Ace 10	7				

Temp0 : temperature at first dose (0 hrs)
$T_{\Delta Tempmax}$: time of maximum temperature decrease
C_{max} : maximum plasma concentration of drug
T_{cmax} : time of maximum plasma concentration of drug
$T_{1/2}$: elimination half time

Table 2a – Randomized double blind **single** dose studies of Ibuprofen (Ibu) and Acetaminophen (Ace)

Author	Doses (mg/kg)	Outcome measurements	Significant treatment differences	Adverse events*
Kauffman, 1992 n=37	Ibu 7.5 Ibu 10 Ibu 10	AUC Temp(t) only illustrated	AUC Ibu 7.5, 10 > ACE 10	No adverse reactions
Nahata, 1992 (n=56)	Ibu 5 Ibu 10 Placebo	ΔTemp(max) Temp (0-8 hr) Temp (4-8 hr) (relative) Temp(t) only illustrated	Temp(0-8hr) Ibu 10 > Ibu 5 Temp(4-8hr) Ibu 10 > Ibu 5	Not mentioned
Wilson, 1991 (n=178)	Ibu 5 Ibu 10 Ace 12.5 Placebo	AUC (0-6 hr) ΔTemp(t),ΔTemp(max) %Red(max) ΔTemp(t) only illustrated	AUC(0-6) Ibu 10 > Ibu 5, Ace 12.5 AUC%Eff Ibu 10 > Ibu 5 For all: AUC%Eff ↓ if Temp(t0) ↑	*Ibu 10: 1 transient hypothermia* *Ibu 5: 1 transient hypothermia*
Marriott, 1991 (n=93)	Ibu 0.625 Ibu 1.25 Ibu 2.5 Ibu 5	ΔTemp at 3 hr Temp(t) only illustrated	ΔTemp(t3) ↑ if dose ↓	1 rash (drug related) 6 GI 7 behavioural 5 febrile seizures
Walson, 1989 (n=127)	Ibu 5 Ibu 10 Ace 10 Placebo	Temp(t) (°F) %Red(t) AUC(0-4,0-6,0-8hr)	%Red Ibu 10 > Ace 10 AUC Ibu 10 > Ace 10 %Red for high temp(t0) Ibu 10 > Ibu 5 > Ace 10	Ibu 5 10/32 mild GI Ibu 16/32 resp. Ibu 10 6/28 mild GI Ibu 10 18/28 respiratory tract Ace 10 6/33 mild GI

* : adverse events which are probably disease related are in italics
GI : gastro-intestinal side effects
Temp(t) : temperature at time t
ΔTemp(t) : temperature difference from baseline at time t
AUC : area under the (temperature) curve
%Red : percentage of temperature reduction from baseline towards 37°C

Table 2b – Randomized double blind **multiple** dose studies of Ibuprofen (Ibu) and Acetaminophen (Ace)

Author	Doses (mg/kg)		Outcome measurements	Significant treatment differences	Adverse events*
Sidler, 1990 n=90 25 hrs	Ibu 7 Ibu 10 Ace 10	8hrly if temp <38,2°C	. ΔTemp(3h) . Temp(mean) (qualitative) . Temp(t) only illustrated	. ΔTemp(3h) Ibu7,10 > Ace10 . Temp(mean) Ibu7,10 < Ace10	3/30 Ibu7 1/29 Ibu10 2/30 Ace10 } not further specified
Walson, 1992 n=64 48 hrs	Ibu 2.5 Ibu 5 Ibu 10 Ace 10	6hrly	. %Red(mean) . %Red(6h) . AUC	. %Red(6h) Ibu10,Ace15 > %Red(6h) Ibu2,5,5 . AUC Ibu2.5 < others	. *1/15 Ibu 2.5 GI (withdrawn)* . 7/45 Ibu all GI . 2/45 Ibu all mild neutropenia . *3/16 Ace15 hypothermia + GI (withdrawn)*
Autret, 1994 n=154 12 hrs	Ibu 7.5 Ace 10	6hrly	. %Red AUC . ΔTemp(4h) . %Red(4h) . time at Temp(min)	%Red(4h) Ibu > Ace	. Ibu 7.5 (n=77) 5 GI, *3 rash, 1 epistaxis* . Ace 10 (n=77) 2 GI, 2 rash, 1 GI, *2 GI*
Esch, 1995 n=70 24hrs	Ibu 5 Ace 10	6hrly	. Temp(4h) . Temp(mean) . Temp(max) . Temp(t)	Temp(4h) Ibu > Ace	. Ibu5 (n=35): 2 FS, 1 exanthema, 1 insomnia, *2 hypothermia* . Ace10 (n=35): 3 FS, 2 exanthema, 2GI, 1 hypothermia

* : adverse events which are probably disease related are in italics
GI : gastro-intestinal side effects
Temp(t) : temperature at time t
ΔTemp(t) : temperature difference from baseline at time t
AUC : area under the (temperature) curve
%Red : percentage of temperature reduction from baseline towards 37°C

Colofon

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