PATHOGENESIS, PREVENTION
OF RECURRENCES AND
OUTCOME OF FEBRILE
SEIZURES

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Abstract

Febrile seizures (FS) occur in 2–5% of children. Their pathogenesis is unknown. Elevated levels of prostaglandins (PG) have been found in cerebrospinal fluid after such seizures, and a third of all patients have recurrences. No safe ways of reducing the risk of recurrences have been found. The outcome has been shown in prospective studies to be good, by they have been linked to mesial temporal sclerosis (MTS) in patients with severe temporal lobe epilepsy (TLE).

The aim was to analyze the records on the role of PGs in the pathogenesis of FS, to find risk factors for recurrences that are amenable to intervention and to evaluate the prevention of recurrences and the connection of FSs with MTS.

We performed a systematic review of the effect of PGs and their synthetase inhibitors on seizures and a meta-analysis of the prevention of recurrences. The prophylactic effect of diazepam and acetaminophen on recurrences was evaluated in a placebo-controlled trial with 180 FS patients, and risk factors for recurrences were analysed from these data. To find MTS, MRI volumetry was performed after 12 years of follow-up on 64 cases chosen out of 329 unselected FS patients: twenty-four with a prolonged initial seizure, eight with a later unprovoked seizure and 32 age, sex and handedness-matched controls.

PGD2, PGE1 and PGE2 had mainly anticonvulsive effects and PGF2alfa proconvulsive ones. NSAIDs had seizure-modulating effects in adult animals ranging from attenuation to provocation. Each degree of increase in fever doubled the recurrence risk, and each febrile episode increased it by 18%. The meta-analysis showed phenobarbital and valproate to prevent recurrences, but they cannot be recommended for FS as they have severe side-effects. The meta-analysis nullified the alleged effect of diazepam, and neither this nor acetaminophen prevented recurrences in a clinical trial. No MTS was found in any patient group.

PGs may be involved in the pathogenesis of FS. No safe prophylaxis for recurrences is available, although the effect of antipyretics needs further evaluation. Measures to reduce feverish infections in order to prevent FS recurrences seem logical. MTS is uncommon even after prolonged FS.

Keywords: acetaminophen, antiepileptic drugs, antipyretic agent, diazepam, febrile seizure, mesial temporal sclerosis, prostaglandin
To Tatu and Antti
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Abbreviations

95% CI 95% confidence interval
COX cyclo-oxygenase
CSF cerebrospinal fluid
EEG electroencephalogram
FS febrile seizure
HHV-6 human herpes virus-6
IL interleukin
MES maximal electroshock
MRI magnetic resonance imaging
MTS mesial temporal sclerosis
PG prostaglandin
OR odds ratio
PTZ pentylenetetrazole
RR risk ratio
SPGR spoiled gradient echo
SPSS Statistical Package for Social Sciences
T1 longitudinal relaxation time
T2 transverse relaxation time
TLE temporal lobe epilepsy
TNFalfa tumour necrosis factor alpha
List of original publications


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1 Introduction

Febrile seizures (FSs) are experienced by 2-5% of all children, and almost a third will suffer from further recurrences (Nelson & Ellenberg 1978, Verity et al. 1985a). FSs are frightening for the families, and over 80% of parents have been reported to fear the death of the child during the initial attack (Baumer et al. 1981). FSs do not have adverse effects on intelligence or learning abilities (Ellenberg & Nelson 1978, Verity et al. 1985b). The risk of epilepsy is 2-3% in a child experiencing a FS, which is higher than the < 1% risk of epilepsy in children with no FSs (Nelson & Ellenberg 1976, Verity & Golding 1991, Berg & Shimmar 1996).

The pathogenesis of FSs is unknown. The role of prostaglandins (PGs) in fever initiation is evident, as inhibitors of PG synthesis effectively block the coordinated febrile response to cytokine signals such as IL-1 (Saper & Breder 1994). Löscher and Siemes (1988) reported an increase in PGE2 levels in CSF during fever and after FS compared with an afebrile state, and the concentrations of PGF2α in CSF have been shown to be over fivefold after FS compared with unprovoked seizures (Tamai et al. 1983). The seizure-modulating effects of endogenous PGs in animals have ranged from inhibition to provocation (Climax & Sewell 1981, Rosenkranz & Killiam 1981). The PG system in the brain may be involved in FSs. PG synthetase-inhibiting drugs are used as antipyretics in children, but their influence on PG production in the brain and on seizure susceptibility in humans is unknown.

Prevention of FS recurrences is desirable at least from the parental standpoint. A young age at the initial FS and a family history of FS have been reported to increase the risk of recurrence (Berg et al. 1992), but it is only the finding of risk factors that are amenable to intervention that can provide measures for protecting children from further recurrences.

The effect of continuous anti-epileptic medication, i.e. phenobarbital and valproate, on recurrences has been demonstrated (Camfield et al. 1980, Mamelle et al. 1984), but their prophylactic use for preventing FS recurrences is restricted by their side-effects (Committee on Drugs 1982, Farwell et al. 1990). The effect of intermittent diazepam has not been clear in clinical trials (Knudsen & Vestermark 1978, Autret et al. 1990, Rosman et al. 1993). As a high fever increases the risk of FSs (Rantala et al. 1995), the use of antipyretic drugs has seemed to offer a solution for preventing recurrences, but their effect has not been properly evaluated and there is no evidence of any prophylactic

Retrospective studies have shown that mesial temporal sclerosis (MTS) occurs more often and is more severe among temporal lobe epilepsy (TLE) patients with previous FSs than in ones with no such history, so that a causal relation has been suggested (Cendes et al. 1993, Trenerry et al. 1993). This is in contradiction to the good clinical outcome reported for FSs (Nelson & Ellenberg 1978, Verity et al. 1985b).
2 Review of the literature

2.1 Definition of febrile seizures

FSs usually occur between 3 months and 5 years of age. They are associated with fever, but without evidence of intracranial infection, a defined cause or previous non-febrile seizures (Consensus Development Conference on Febrile Seizures 1980). Most FSs are single generalized seizures of duration less than 15 minutes, but 10–30% are complicated, i.e. prolonged (duration more than 15 minutes), multiple (with a recurrence within 24 hours) or having focal features (Nelson & Ellenberg 1978, Verity et al. 1985a, Knudsen 1990). FSs have a good prognosis and are to be distinguished from epilepsy, which is characterized by recurrent unprovoked seizures (Consensus Development Conference on Febrile Seizures 1980). Since fever can provoke seizures in epileptic patients at any age, an initial seizure occurring during fever can also be the first manifestation of epilepsy, but one seizure with or without fever never justifies a diagnosis of epilepsy.

2.2 Occurrence of febrile seizures

The occurrence of FS in Western Europe and the United States is 2-5% (Nelson & Ellenberg 1978, Verity et al. 1985a, Forsgren et al. 1990b). Nelson and Ellenberg (1978) observed a statistically significant difference between black and white children in this respect in a national cohort study (4.25% vs. 3.5%). The occurrence of FSs in Japan has been 7% (Knudsen 1990). Most population-based studies have not found any significant effect of gender (Nelson & Ellenberg 1978, Verity et al. 1985a, Knudsen 1990). In nearly 90% of cases the age at the onset of FSs is less than three years, and half of the patients experience their first FS during the second year of life (Verity et al. 1985a).

In a meta-analysis of 14 evaluations of the predictors of recurrences, Berg et al. (1990) reported the average recurrence rate for FSs to be 34.3%, the risk of several recurrences being 16%. Half of the recurrences are reported to occur within six months of the initial FS and three quarters within a year (Nelson & Ellenberg 1978). A first FS at an age of
less than one year doubled the risk of recurrences relative to a first attack later on. Young age has also been found to be the most powerful risk factor for multiple recurrences (Berg et al. 1990).

2.3 Aetiology and pathogenesis of febrile seizures

2.3.1 Family history

Berg et al. (1995) reported that children having a FS had an odds ratio (OR) of 6.5 for a positive family history of FS in first-degree relatives and 3.6 in second or higher-degree relatives compared with children with no history of FSs. A positive family history of FS nearly triples the risk of recurrences, but there is no evident influence of unprovoked seizures in family members on the recurrence rate (Berg et al. 1990). The inheritance of FS has been thought to be multifactorial and polygenic (Forsgren et al. 1990a).

2.3.2 Fever and febrile seizures

Each additional degree of body temperature above 101°F (38.3°C) almost doubled the risk of FS in the series of Berg et al. (1995) (OR 1.8, p <0.001), and Rantala et al. (1995) likewise reported that children with FS had a higher body temperature both at the time of hospital admission and during the first three days in hospital than age and sex-matched controls with a feverish infection without seizures (p <0.01).

The lower the body temperature during the initial FS, the greater is the risk of recurrences (El-Radhi & Banajeh 1989, Berg et al. 1992, Offringa et al. 1992), so that each degree of increase in body temperature during the first seizure reduces the recurrence risk by 18% (RR 0.82, 95%CI 0.69-0.97) (Berg et al. 1992).

To evaluate the connection between the duration of fever prior to the initial seizure and recurrences, Berg et al. (1992) compared recurrences between children with fever lasting less than an hour, from one to 24 hours and more than 24 hours. The risk of recurrences decreased as the duration of fever prior to the first FS increased (RR 0.4, 95%CI 0.35-0.66).

FSs mostly occur during fever caused by common viral agents (Lewis et al. 1979, Rantala et al. 1995). Rantala et al. (1995) pointed to two significant differences in the clinical diagnosis between their FS and control groups, the latter having more pneumonia (9% vs. 0%) while the former had more exanthema subitum (9% vs. 0%), and speculated that the difference in clinical symptoms between the groups was partly due to patient selection, as the paediatric outpatient clinic mainly treats children referred from primary health care. Exanthema subitum is caused by human herpes virus 6 (HHV-6). Barone et al. (1995) suggested that primary HHV-6 infection might be important in the first FS, and it has also been suspected to increase the risk of recurrences (Kondo et al. 1993). These assumptions have not been confirmed in a prospective setting, however. Similarly,
patients with a first FS did not have a higher incidence of HHV-6 infection than age-matched controls (Hukin et al. 1998), nor were any differences in FS recurrence rates observed when patients with an initial FS during HHV-6 infection were compared to those presenting during an infection caused by other pathogens (Jee et al. 1998). Thus HHV-6 does not seem to have any special role in the pathogenesis of FS or its recurrences relative to other fever-causing pathogens.

Knudsen (1988) showed that children experiencing four or more fever episodes per year after a FS had a higher recurrence rate than children with up to three fever episodes a year (78\% vs. 17\%), and child care in a nursery group compared to home day-care was also reported to increase the recurrence rate from 37\% to 45\% when the children were followed up for 18 months after the first FS (Knudsen 1985). Children under two years of age have been shown to have a higher risk of respiratory infections in day-care centres than if taken care of at home, and it is likely that the increase in the number of infectious contacts leads to more frequent feverish infections. The increase in the adjusted RR for respiratory infections in day-care centres has been highest in one-year-old children, being 1.69 (95\%CI 1.43-2.01) for common colds, 1.99 (95\%CI 1.57-2.52) for otitis media and 9.69 (95\%CI 3.31-40.55) for pneumonia (Louhiala et al. 1995). Half of all FSs are experienced during the second year of life (Verity et al. 1985a), and thus day care at home or in small groups might reduce the risk of their recurrence, but the hypothesis has not been tested.

### 2.3.3 Prostaglandins and cytokines in febrile seizures

Infective agents initiate an inflammatory reaction and PG synthesis in many tissues, including the central nervous system. The substrates for PG synthesis are phospholipids, which are converted to arachidonic acid by the enzyme phospholipase. Cyclo-oxygenase enzymes (COX-1 and COX-2) convert arachidonic acid to a PG precursor, which is converted to various PGs by specific PG synthetases (Vane et al. 1996). Several endogenous PGs are produced in the brain (Seregi et al. 1985). PGs have a major role in elaborating fever. PGE2 at least has pyrogenic activity, but other arachidonic acid metabolites may also contribute to body temperature regulation (Saper & Breder 1994). The levels of arachidonic acid and PGs are low in the mammalian brain under normal conditions (Wolfe & Mamer 1975), the highest basal concentrations of PGD2 and PGF2alpha in animal brains (although relatively low) having been found in the hypothalamus and cerebral cortex and lower concentrations in the cerebellum, medulla and hippocampal formation (Seregi et al. 1985).

It has been shown using MES or chemical induction of seizures in animal models that the concentrations of endogenous PGs increase in the brain under such conditions (Steinhauer & Hertting 1981, Förstermann et al. 1982, Navarro et al. 1989), the most prominent rise being observed in PGD2 concentration, followed by PGF2alpha and other PGs (Förstermann et al. 1982). The effect of PGs on seizures is controversial, since different PGs may have both provoking and inhibiting effects (Climax & Sewell 1981, Rosenkranz & Killam 1981). Tamai et al. (1983) compared the PGF2alpha levels in CSF after a FS (31 cases) or an epileptic seizure (32 cases) or during a non-neurological
disease (20 cases) and found them to be higher in patients with a FS (mean 207.8, SE 50.7 pg/ml vs. 43.0, SE 4.6 in those with an epileptic seizure and 53.3, SE 8.7 pg/ml in those with a non-neurological disease). Löscher and Siemes (1988) reported eight times higher PGE2 concentrations in CSF after a FS (17 cases) than for afebrile children (9 cases), but the difference between the FS cases (mean 101, range 15-190 pg/ml) and 12 cases with fever and no seizures (mean 66, range 3-224 pg/ml) was not statistically significant. Linear regression analysis gave a significant positive correlation between PGE2 concentration in the CSF and body temperature (p<0.001). The authors state that it is not clear whether the increased concentrations of PGE2 in the CSF after FS is due to the seizure or solely related to the febrile state of the child.

Cytokines, soluble proteins or glycoproteins that act as chemical communicators between cells and as inflammatory mediators, but not as effecting molecules, are produced in leukocytes and other affected cells during infection or aseptic inflammation (Callard & Gearing 1994, Saper & Breder 1994). One specific cytokine often has several target cells and biological activities, and the cytokines have been shown to have a profound effect on leukocyte migration and function, haematopoietic cells, temperature regulation, acute phase reaction, tissue remodelling and cell survival (Callard & Gearing 1994). Interleukin–1beta (IL-1beta) has been shown to act as the predominant endogenous pyrogen in the fever reaction caused by pox-virus infection in mice (Alcami & Smith 1996), its effect evidently being linked to PG synthesis, as it is reduced by PG synthetase inhibitors (Ushikubi et al. 1998). Although several other cytokines (IL-1alfa, IL-6, TNFalfa, interferons) have been implicated, their role in fever pathogenesis has remained unclear (Saper & Breder 1994, Licinio & Wong 1996).

The level of IL-1beta in plasma is increased acutely after a FS relative to children with fever alone (Ichyama et al. 1998, Tutuncuoglu et al. 2001), and IL-1beta production by lipopolysaccharide (bacterial endotoxin)-stimulated blood monocytes in vitro is also enhanced after a FS relative to the situation in children with fever but no seizures (Helminen & Vesikari 1990). Concentrations of IL-1beta and other cytokines (IL-1alfa, IL-6 and TNFalfa) have not been found to be increased in the CSF of patients with FS compared with feverish children without seizures, but elevated concentrations have been related to encephalitis and encephalopathy (Ichyama et al. 1998).

It is not clear how the effect of IL-1beta and other possible endogenous pyrogens is mediated from peripheral tissues to the central nervous system, where they stimulate PG synthesis during inflammatory states. One theory suggests a transport system for cytokines through the blood-brain barrier (Licino & Wong 1996), while Saper and Breder (1994) state that they may reach the brain tissue through circumventricular organs, which are specialized areas along the cerebral ventricular surface that have no blood brain barrier. The circumventricular organ located near the thermoregulatory centre in the hypothalamus is the organum vasculosum, and this is thought to be important in fever pathogenesis. As a fever reaction develops rapidly after systemic administration of IL-1beta, it is also possible that a neuronal pathway may contribute to fever initiation. Nervus vagus stimulation by either IL-1beta or lipopolysaccharide, which is a bacterial endotoxin, increases production of the fever mediator PGE2 in the anterior hypothalamus, a reaction which has been shown in an animal model to be inhibited by vagotomy (Blatteis & Sehic 1997).
2.4 Prevention of recurrences

In the light of the benign nature of FS, the prevention of recurrences is aimed chiefly at alleviating the symptoms and reducing parental anxiety. Continuous anti-epileptic medication with phenobarbital has been widely used since the first report of its efficacy in preventing FS recurrences (Faero et al. 1972), in which children having a mean serum phenobarbital concentration of 16-30 mg/l during follow-up had a significantly lower rate of recurrences (4% vs. 21%) than those with a mean serum concentration of 8-15 mg/l. Correspondingly, Mamelle et al. (1984) found that one out of 22 patients receiving valproate (4.5%), four out of 21 treated with phenobarbital (19.0%) and 9 of 26 in a placebo group (34.6%) had recurrences. In the meta-analysis by Newton (1988) both phenobarbital and valproate were ineffective in preventing recurrences, but only one out of the seven studies analysed had been randomized and placebo-controlled. Children assigned to daily phenobarbital after a FS have been shown to have a mean IQ 5.2 points lower than placebo-treated children six months after discontinuation of the drug (Farwell et al. 1990), and as valproate can potentially cause severe fatal pancreatitis and hepatitis (Committee on Drugs 1982), neither can be recommended as preventive treatment for benign FSs at present. Both carbamazepine and phenytoin have proved ineffective for preventing recurrences (Bacon et al. 1981, Antony & Hawke 1983).

The findings on the effect of diazepam administered during fever on recurrences of FSs have been controversial. Intermittent diazepam was found to be effective in one placebo-controlled study (Rosman et al. 1993) and in two trials in which it was compared with continuous phenobarbital or no therapy at all (Knudsen & Vestermark 1978, Knudsen 1985). One placebo-controlled study showed no effect of diazepam in preventing FS recurrences (Aubert et al. 1990).

High fever markedly increased the rate of recurrences (Berg et al. 1995, Rantala et al. 1995). Antipyretic agents are routinely given to sick children who have a history of FS, to reduce the fever and hence (theoretically) the likelihood of recurrences (Baumann & Duffner 2000). Regular administration of acetaminophen (15-20 mg/kg x 6) has not been found to prevent early recurrences of FS, however, or to affect the occurrence or height of fever as compared with sporadic administration (Schnaiderman et al. 1993).

2.5 Outcome of febrile seizures

The occurrence of epilepsy after a FS is 2-3%, which is higher than the figures of 0.4-1% reported among children with no FS (Nelson & Ellenberg 1976, Verity & Golding 1991, Berg & Shinnar 1996). The distribution of epilepsy by subtypes, including TLE, has been found to be similar in patients with FS and the rest of the population (Verity & Golding 1991), and it has been stated that FSs are not likely to cause permanent brain damage or lead to unprovoked seizures. The increased prevalence of epilepsy after FS can be explained by the ability of fever to trigger seizures in general. In a situation like this the first manifestation of epilepsy is recorded as FS.
Complex features in the initial FS have been reported to increase the risk of recurrences up to nine-fold, with each recurrence adding 65% to the risk of unprovoked seizures (Verity & Golding 1991, Berg & Shinnar 1996). Since these studies included children with neurological problems, the confounding factors make interpretation difficult. Previous neurological or developmental problems increased the risk of unprovoked seizures to 35% (Berg & Shinnar 1996) and both complicated FSs and neurodevelopmental abnormality have been shown to be more common in patients with recurrences (Verity et al. 1998).

FSs are said to have no adverse effects on the long-term intellectual and behavioural outcome, even for patients with a complex initial attack and recurrences (Ellenberg & Nelson 1978, Knudsen et al. 1996, Verity et al. 1998).

2.5.1 Mesial temporal sclerosis

Mesial temporal sclerosis (MTS) is a disease of the limbic system in which the hippocampal formation is the most profoundly affected structure, so that it is often termed hippocampal sclerosis, or Ammon’s horn sclerosis. Falconer et al. (1974) have performed an en-bloc dissection of the affected temporal lobe on hundreds of patients with drug-resistant epilepsy and found MTS in about half of the cases. In a series of 30 children with TLE undergoing temporal lobectomy, 20 had MTS, of whom 15 had a history of FS, compared with one case among the 10 patients with no MTS (Falconer 1974). Numerous studies have suggested that TLE patients with a history of FS have more frequent and more intense sclerotic changes in mesial structures than TLE patients with no FS background (Kuks et al. 1993, Cendes et al. 1993, Harvey et al. 1995, Free et al. 1996, Barr et al. 1997, Marsh et al. 1997, Theodor et al. 1999), whereas only a few published reports have failed to find such a connection (Lawson et al. 1997, Salmenperä et al. 1998). All the studies pointing to a connection between FSs and MTS have been retrospective and their patients selected (severe cases of TLE).

VanLandingham et al. (1998) reported a high incidence of hippocampal intensity or volume changes in MRI immediately after a complicated FS (in 10 out of 27 cases). Since the patients had a high incidence of abnormalities in their developmental status (22%), the patients in this survey, too, may be regarded as selected.

There are no studies evaluating the occurrence of MTS in unselected FS patients, let alone ones in which the status of the temporal structures is reported, so that there is no true evidence to support the speculated causal relation between FSs and MTS.
3 Aims of the research

1. To study the literature on prostaglandins and seizures in order to clarify the possible role of prostaglandins in febrile seizure pathogenesis.
2. To evaluate risk factors for recurrence of febrile seizure and the prevention of such recurrences.
3. To evaluate whether febrile seizures cause mesial temporal sclerosis.
4 Material and methods

4.1 Structure of the research

This thesis is based on five original publications (I-V). The role of PGs in the pathogenesis of FS is discussed in a systematic review of the effects of these and their synthetase inhibitors on seizures (I). To find new ways of reducing the risk of recurrences of FS, we reviewed the literature on the medical prevention of recurrences (III) and analysed and quantified the effects of those risk factors for recurrences that were amenable to intervention (II) in a randomized, double-blinded, placebo-controlled prophylactic treatment trial with diazepam and acetaminophen (IV). The occurrence of MTS in FS patients was studied by MRI-volumetry in an assessment of the long-term outcome (V).

4.2 Methods for the review of prostaglandins and their synthetase inhibitors in relation to seizures

The aim of this systematic review of the role of PGs and their synthetase inhibitors with respect to FSs was to examine all the experimental and human clinical studies dealing with seizures and endogenous PGs or their synthetase inhibitors published in English. We performed a literature search using the Medline database using the keywords “seizure”, “convulsion” or “febrile seizure” and “prostaglandin”, “prostaglandin antagonist” or “prostaglandin inhibitor” to find the previously published data. All suitable articles known to us before the computer search were included, and the references of the newly identified ones were reviewed to ascertain that all relevant articles had been found. All the authors read the articles independently and analysed them using a predesigned data collection sheet.

Altogether 68 articles on the role of endogenous PGs and PG inhibitors in seizures were found and reviewed. Thirty-one of these were original works evaluating the effect of PGs and/or their inhibitors on seizures, and were included in our systematic review.
Initially our aim was to make a meta-analysis of the available literature, but the diversity of the published articles and the lack of detailed original data made this impossible. Thus the results were introduced in the form of a systematic review and tabulated without summarizing them in the form of a synthesis.

4.3 Subjects and methods in the prophylactic treatment trial and the study of risk factors for recurrences

4.3.1 Subjects

All children from the primary catchment area of Oulu University Hospital are sent to the Department of Paediatrics after the first FS. The parents of those children treated at the Department of Paediatrics in that hospital for their first FS between November 1986 and September 1990 were offered the opportunity of participating in a 2-year follow-up treatment trial. The parents of all but three patients accepted, and only those patients who were unable to attend the final 2-year follow-up visit subsequently had to be excluded. The eligibility criteria for the treatment trial were no previous seizures, no anticonvulsant medication, no progressive neurological disease, no intracranial infection and no chronic disease requiring continuous medication.

4.3.2 Treatment protocol

The calculation of the sample size needed for the treatment trial was based on previous findings of a recurrence rate of 20% in our earlier febrile seizure surveys. A reduction to 5% was regarded as clinically important. For a power of 80% and a type I error of 0.05, the calculated sample size for each group was 66 children. To ensure eventual samples of this size, we included 90 patients in each anticonvulsive treatment group. Thus the total number of children needed for the treatment trial was 180.

The participants were randomly assigned to receive either a placebo or diazepam during all their febrile infections, employing blocks of varying sizes of four, six, or eight patients within each stratum. Only the biostatistician knew the details of the randomization schedule.

The medication was started with a single dose of diazepam or placebo solution for rectal use (rectiol) when the body temperature exceeded 38.5°C. The dosage of diazepam was 2.5 mg for children weighing less than 7 kg, 5 mg for children weighing from 7 to 15 kg and 10 mg for children weighing more than 15 kg. Six hours after receiving the rectiol the medication was continued with oral diazepam doses of 0.2 mg/kg or placebo solution three times a day for the first two days if the child was still feverish (Fig. 1).
Fig. 1. Randomization of patients into groups for prophylactic anticonvulsive medication (diazepam and placebo) during all subsequent fever episodes and for antipyretic treatment (acetaminophen and placebo) during the first fever episode. The assignment to acetaminophen or placebo was switched after each fever episode.

The first febrile episode was assigned randomly to management with an oral solution of acetaminophen or placebo, the assigned treatment then being switched after each febrile episode (Fig 1). The dose of acetaminophen was 10 mg/kg four times per day.

The dosage was adjusted according to changes in the body weight of the child during the 2-year follow-up. If the child’s temperature exceeded 40°C the parents were allowed to give extra acetaminophen 10 mg/kg. If a FS occurred, it was treated with a diazepam rectiol and the medication was stopped.

The study was double-blinded. The final analysis included febrile events in four subgroups defined according to the assigned treatment, i.e. diazepam and acetaminophen, diazepam and placebo, placebo and acetaminophen and two placebos (Fig. 1).

4.3.3 Evaluation and follow-up of the patients

The participants had been examined at the time of the hospitalization for the first FS by the duty physician, who had made a basic evaluation of their neurological and developmental status and recorded the symptoms and signs of infection. The parents were interviewed for background information.

The parents of the 180 patients included in the treatment trial filled in a questionnaire whenever their child was feverish during the 2-year follow-up or if they suspected an unprovoked seizure. The information of interest was the type and timing of the symptoms, the rectal temperature, recorded twice a day during the febrile illness, and the use of the study medication and/or other antipyretics. A nurse contacted the participating families monthly in order to receive all the information on possible infections and to motivate the parents to follow the protocol.
A thorough neurological and developmental evaluation was performed by a paediatric neurologist at the end of the 2-year follow-up, including basic developmental status (height, weight, head circumference), motor and sensory function tests, vision and motor function of the eyes, speech and hearing. An EEG was also taken.

Of the total of 180 patients, 161 were followed up for the 2-year period, 157 came to the last outpatient examination and an EEG was obtained for 156. The final analysis of the efficacy of the drugs was based on data for 153 children who had had at least one febrile episode and had thus used the medication supplied. Additionally, all the available data on the 10 patients who dropped out after 1 to 18 months of the follow-up who had had at least one prospectively followed febrile episode were included in the Kaplan-Meier analysis.

### 4.3.4 Risk factors for recurrences

Baseline information on the 180 children participating in the treatment trial and their final physical, developmental and neurological assessments, the background information from the parental interviews and the prospective follow-up data on each febrile episode during the two-year period were used in the analysis of the risk of recurrence and the short-term outcome.

The 65 girls and 88 boys who had had at least one febrile episode during the follow-up period, at a mean age (range) of 1.7 (0.8 to 4.6) years, were included in the risk factor analysis. The influence of age at enrolment on the rate of FS recurrence was analysed using the age at the time of the initial seizure as a continuous variable. The initial seizure was a complicated one in 49 children. A positive family history of FS was found in 59 children, and 18 had a positive family history of epilepsy. The influence of temperature during the subsequent fever episodes on the recurrence of FS was analysed by calculating the mean of the maximum temperatures during these episodes in the children without further seizures and comparing them with the means of the maximum temperatures of the fever episodes associated with a FS in the children with one or more recurrences.

The data on the 156 children for whom an EEG was obtained at the 2-year follow-up visit were included in the analysis of the effect of recurrences on the short-term outcome.

### 4.4 Meta-analysis of prophylactic treatment against recurrences

To find all existing randomized placebo-controlled studies of the prevention of FSs published in English, we performed a literature search using the Medline database. The preventive treatment trials known to us beforehand were also accepted, and to ensure that all the relevant articles had been found, the references in the accepted papers were reviewed. Altogether we found and reviewed 45 articles for the meta-analysis. All the authors read the articles independently and analysed them using a predesigned data collection sheet. Nine out of the 45 articles filled the criteria for a randomized, placebo-controlled treatment trial.
4.5 Patients and methods in the mesial temporal sclerosis survey

The connection between FSs and MTS was studied in a sample from the 329 unselected FS patients who had participated in our clinical evaluation of the factors triggering the first FS, the risk factors for recurrences and the prevention of recurrences at the Department of Paediatrics, University of Oulu, during the years 1984 to 1990 (Rantala et al. 1990, Rantala et al. 1994, Uhari et al. 1995). The opportunity to participate in the outcome study, including MRI of mesial temporal structures and a neurological evaluation, was offered to the 30 patients with a prolonged initial FS and the eight patients with at least one unprovoked seizure after the first FS. One patient who met both criteria was analysed in the unprovoked seizure group. All the patients with an unprovoked seizure participated, but three patients in the prolonged FS group could not be reached and three others chose not to participate. For each of the 32 cases we selected an age, sex and handedness-matched control patient among those who had had a single simple FS with no recurrences or unprovoked seizures. Out of the eight patients in the unprovoked FS group, three had had complex partial seizures, two had rolandic epilepsy, one had myoclonic seizures, one had several focal secondarily generalized seizures and one had experienced a single unprovoked seizure with secondary generalisation. The mean age (range) of the patients with a prolonged initial FS at the time of the MRI examination was 14.4 (9.9-20.2) years, that of the patients with later unprovoked seizures 12.5 (10.4-14.2) years and that of the controls 14.2 (10.3-20.4) years. The mean follow-up times (range) in these groups were 12.5 (8.5-14.7) years, 11.2 (8.9-12.6) years and 12.5 (9.6-14.7) years, respectively.

The patients or their parents were asked about previous seizures and medical history, scholastic achievements and problems in learning. The hospital records of the participants were reviewed, and a clinical examination was performed, including developmental status, i.e. height, weight, head circumference and Tanner pubertal stage (Tanner & Whitehouse 1976), motor and sensory function tests, visus and motor function of the eyes, speech and hearing.

MRI was performed using a 1.5 Tesla scanner (Signa, EchoSpeed, General Electric Medical Systems, Milwaukee, Wis), obtaining T1-weighted sagittal images together with double fast spin echo T2-weighted axial and coronal slices. The T2-weighted axial images were obtained parallel to the temporal lobes and the coronal images perpendicular to them. A 3D coronal SPGR series was also obtained, providing high grey matter and white matter contrast, and transferred to a workstation for volumetry. Reformatted images two millimetres thick were generated perpendicular to the hippocampal formations, and the volumes of both the amygdala and the hippocampal formations were measured on these images by one radiologist who was blinded to the clinical history of the subjects. The boundaries of the structures concerned were defined according to previous reports (Watson et al. 1992). The in-house software used for this employs a semi-automated technique combining tracing and a threshold. All the MR images were also evaluated visually by two radiologists, first separately and then together, to reach a consensus. Special attention was paid to the size, shape and signal intensity of the hippocampal formations.

Since there are no normal values for adolescent patients, we used the findings in our control group, i.e. the patients with a single simple FS, as a source for reference values.
The right-left hippocampal volume difference threshold values in our adolescent control patient group (2 SD range) were –0.13 cm³ and 0.49 cm³.

4.6 Ethical considerations

The protocols were approved by the ethical committee of the Medical Faculty of the University of Oulu, and informed consent was obtained from a parent or the patient at the beginning of each phase of the research.

4.7 Statistical methods

SPSSWin versions 6 and 9 were used to analyse the data.

The relative risk for each recurrence factor was calculated separately and a multivariate risk factor analysis was performed using the Cox proportional-hazard model. The effect of recurrences on the outcome was analysed by logistic regression.

In the treatment trial the frequency of recurrences of FS in the patients receiving diazepam was compared with that in the placebo group. The effect of acetaminophen was evaluated during each fever episode separately in numerical order by comparing the frequency of recurrences in patients receiving acetaminophen with those in patients receiving the placebo during the episode in question, and the frequency of recurrences during all the episodes treated with acetaminophen was also compared with that in the episodes with placebo treatment. The differences in the frequencies of recurrences of FS between the patient groups and between the fever episodes were analysed with the chi-square test. The times to first recurrence in these strata were assessed by the Kaplan–Meier method. The cumulative incidence curves for recurrences during the two-year follow-up were compared between the groups with the log-rank test.

The mean absolute volumes of the hippocampal formation and amygdala and the mean right-left volume difference in the hippocampal formations were compared between the groups using a one-way analysis of variance. In the case of a statistically significant difference, the analyses were continued using Bonferroni Post Hoc multiple comparison. The Kruskal-Wallis test was used to compare the number of patients with problems in school performance or abnormal neurological findings between the groups. The significance of a difference between two parametric variables was assessed by the t-test.

The meta-analysis of preventive treatment was performed by combining the original data for each treatment modality considered. A test of heterogeneity was performed on the total set of papers before combination of the data (Thompson 1994). The children with recurrences were regarded as treatment failures. The weighted average risk was calculated using the inverse of the variance attached to the risk in each paper as the weight (random effect model) (Hedges 1994). 95% confidence intervals were calculated for the odds ratios, and the Mantel-Hazael chi-square test was used to assess their statistical significance. The effect of each treatment modality was reported in terms of the number of patients needed to treat to prevent a FS recurrence, and 95% confidence intervals were calculated where the efficacy of treatment was statistically significant.
5 Results

5.1 Endogenous prostaglandins, prostaglandin synthetase inhibitors and seizures

The original six articles on the seizure modulating effects of various PGs in humans were reports on extra-amniotic or intra-amniotic PGE2 or PGF2alpha administered to induce abortion (Lyneham et al. 1973, MacKenzie et al. 1973, Fraser & Gray 1974, Shearman et al. 1975, Faden et al. 1976) or intravenous or oral PGE2 or PGF2alpha for the induction of labour (Thiery et al. 1974). All five major seizures reported in relation to PG administration occurred in the series described by Lyneham et al. (1973), in which 320 women had received intra-amniotic PGF2alpha for the induction of abortion.

There were 13 articles evaluating the effect of endogenous PGs on chemically or electrically induced seizures, and 12 that of PG synthetase inhibitors. All the experiments had been conducted with adult animals.

Intracerebroventricular or intraperitoneal administration of PGD2, PGE1 or PGE2 prior to seizure induction increased the latency of the onset of seizure and/or reduced the seizure incidence, and thus had an anticonvulsant effect (Rosenkranz & KiIlam 1979 and 1981, Climax & Sewell 1981, Förstermann et al. 1983). These PGs did not have any effect on seizures caused by kindling (Croucher et al. 1991). The effect of intracerebroventricular PGF2alpha was controversial, being said in one paper to have inhibited pentylenetetrazole (PTZ)-induced seizures (Förstermann et al. 1983) and in two others to have promoted seizures induced either by PTZ or maximal electroshock (Climax & Sewell 1981, Rosenkranz & Killam 1981) (Table 1).

Twelve evaluations of the effect of non-steroidal anti-inflammatory drugs (NSAIDs), i.e. PG synthetase inhibitors, on seizures in experimental animals have shown the most powerful inhibitors of cyclo-oxygenase (COX) enzymes, diclofenac, flurbiprophen and indomethacin, to either promote chemically or electrically induced seizures or to have no effect on them when administered by either an intramuscular or intraperitoneal route (Steinhauer & Hertting 1981, Förstermann et al. 1982, Wallenstein & Mauss 1984). It is interesting that acetylsalicylate, which is the least potent inhibitor of COX enzymes among the NSAIDs tested, promoted seizures induced with both maximal electroshock...
and PTZ in one trial (Climax & Sewell 1981). Other less potent COX inhibitors, ibuprofen, mefenamic acid, meclofenamic acid, acetaminophen and sulindac, had mainly inhibitory effects on seizures induced with PTZ, penicillin and flurothyl (Wallenstein & Mauss 1984, Wallenstein 1987), but no effect on those induced by maximal electroshock (Wallenstein & Mauss 1984) (Table 2).

Table 1. Effects of certain prostaglandins (PG) on chemically or electrically induced seizures in adult animals.

<table>
<thead>
<tr>
<th>PG</th>
<th>Route of administration</th>
<th>Dosage (µg)</th>
<th>Seizure induction</th>
<th>Animal</th>
<th>Number of animals with PG</th>
<th>Controls Effect on seizure</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>D2</td>
<td>Amygdala</td>
<td>1–10</td>
<td>Kindling</td>
<td>Rat</td>
<td>9</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>2–20</td>
<td>PTZ</td>
<td>Rat</td>
<td>71</td>
<td>124</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>E1</td>
<td>ICV, IP</td>
<td>0.5–60</td>
<td>PTZ</td>
<td>Rat, mouse</td>
<td>96</td>
<td>118</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV, IP</td>
<td>1–320</td>
<td>MES</td>
<td>Rat, mouse</td>
<td>130</td>
<td>110</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>IP</td>
<td>0.6–50</td>
<td>STR</td>
<td>Mouse</td>
<td>104</td>
<td>104</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>0.5–20</td>
<td>PTX</td>
<td>Mouse</td>
<td>70</td>
<td>70</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>1–30</td>
<td>INZ</td>
<td>Mouse</td>
<td>60</td>
<td>60</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>E2</td>
<td>Amygdala</td>
<td>1–10</td>
<td>Kindling</td>
<td>Rat</td>
<td>15</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>1–160</td>
<td>PTZ</td>
<td>Rat, mouse</td>
<td>168</td>
<td>203</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV, IP</td>
<td>2–320</td>
<td>MES</td>
<td>Rat, mouse</td>
<td>230</td>
<td>210</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>1–40</td>
<td>STR</td>
<td>Mouse</td>
<td>140</td>
<td>140</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>1–50</td>
<td>PTX</td>
<td>Mouse</td>
<td>140</td>
<td>140</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>2–50</td>
<td>INZ</td>
<td>Mouse</td>
<td>120</td>
<td>120</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>12.5–100</td>
<td>FLS</td>
<td>Baboon</td>
<td>6</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>F2alpha</td>
<td>Amygdala</td>
<td>1–10</td>
<td>Kindling</td>
<td>Rat</td>
<td>9</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>20</td>
<td>PTZ</td>
<td>Rat</td>
<td>20</td>
<td>47</td>
<td>Inhibitory</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>10–60</td>
<td>PTZ</td>
<td>Mouse</td>
<td>10</td>
<td>10</td>
<td>Promoting</td>
</tr>
<tr>
<td></td>
<td>ICV</td>
<td>10–60</td>
<td>MES</td>
<td>Mouse</td>
<td>100</td>
<td>60</td>
<td>Promoting</td>
</tr>
</tbody>
</table>

Table 2. Effects of prostaglandin synthetase inhibitors (PGSI) on experimentally induced seizures in adult animals.

<table>
<thead>
<tr>
<th>PGSI</th>
<th>Route of PGSI administration</th>
<th>Dosage</th>
<th>Seizure induction</th>
<th>Animal</th>
<th>No. of animals with PGSI</th>
<th>Controls</th>
<th>Effect on seizure</th>
<th>Paper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylate</td>
<td>Oral 100 mg/kg</td>
<td>PIZ</td>
<td>Mouse</td>
<td>8</td>
<td>10</td>
<td>None</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>IM 0.1–33 mg/kg</td>
<td>PIZ</td>
<td>Mouse</td>
<td>80</td>
<td>20</td>
<td>Promoting</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>IM 0.1–10 mg/kg</td>
<td>PIZ</td>
<td>Mouse</td>
<td>400</td>
<td>200</td>
<td>None</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>IM 10 mg/kg</td>
<td>PIZ</td>
<td>Mouse</td>
<td>9</td>
<td>10</td>
<td>Promoting</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>IM, IP 10 mg/kg</td>
<td>PIZ</td>
<td>Rat, mouse</td>
<td>150</td>
<td>150</td>
<td>None</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Indomethacin</td>
<td>IP 0.1–100 mg/kg</td>
<td>PIZ, stress</td>
<td>Mouse, gerbil, rat</td>
<td>547</td>
<td>484</td>
<td>Promoting</td>
<td>1, 3, 8–12</td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>IM, IP 15–50 mg/kg</td>
<td>PIZ</td>
<td>Rat</td>
<td>46</td>
<td>36</td>
<td>None</td>
<td>4, 5</td>
<td></td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>IP 20–150 mg/kg</td>
<td>PIZ</td>
<td>Rat</td>
<td>16</td>
<td>16</td>
<td>Inhibitory</td>
<td>5, 7</td>
<td></td>
</tr>
<tr>
<td>Meclofenamic acid</td>
<td>IP 60 mg/kg</td>
<td>PIZ</td>
<td>Rat</td>
<td>6</td>
<td>–</td>
<td>Promoting</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>IP 15–50 mg/kg</td>
<td>PIZ</td>
<td>Rat</td>
<td>8</td>
<td>8</td>
<td>Inhibitory</td>
<td>5, 6</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>IM, IP 30–300 mg/kg</td>
<td>PIZ</td>
<td>Rat, mouse</td>
<td>70</td>
<td>77</td>
<td>None</td>
<td>1, 4, 5</td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td>IP 15–150 mg/kg</td>
<td>PIZ</td>
<td>Rat</td>
<td>49</td>
<td>40</td>
<td>None</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sulindac</td>
<td>IP 50–150 mg/kg</td>
<td>PIZ</td>
<td>Rat</td>
<td>24</td>
<td>20</td>
<td>Inhibitory</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

BI, bicuculline; FL, flurothyl; ICV, intracerebroventricular; IM, intramuscular; IP, intraperitoneal; MES, maximal electroshock; PN, penicillin; PIZ, pentylenetetrazole; PTX, picrotoxin; NA, not available; 1, Steinhauer & Hertting 1981; 2, Climax & Sewell 1981; 3, Förstermann et al. 1982; 4, Wallenstein 1991; 5, Wallenstein & Mauss 1984; 6, Wallenstein 1985; 7, Wallenstein 1987; 8, Steinhauer et al. 1979; 9, Förstermann et al. 1984; 10, McGinley et al. 1985; 11, Seregi et al. 1984; 12, Simmet & Tippler 1990
5.2 Risk factors, prognosis regarding recurrences and results of the treatment trial

5.2.1 Occurrence of fever episodes and seizures during follow-up

There were altogether 642 febrile episodes and 55 FS recurrences during the two-year follow-up. Thirty-eight patients had at least one recurrence and 11 experienced multiple recurrences. Fifteen had a FS recurrence during their first febrile event, and 32 had a recurrence within one year of the initial FS. Two patients experienced an unprovoked seizure during the follow-up.

5.2.2 Risk factors and the prognosis regarding recurrences

The multivariate risk factor analysis showed the number of febrile episodes and the degree of fever during the subsequent febrile episodes to have a statistically significant influence on the recurrence rate. Each febrile episode increased the risk of recurrence by 18% (RR 1.2, 95% CI 1.1-1.3, p = 0.0003) and each degree of increase in body temperature during the subsequent fever episodes almost doubled the recurrence risk (RR 1.9, 95% CI 1.0-3.7, p = 0.04). A high temperature during the initial FS did not significantly reduce the risk of recurrences, but it had a low risk ratio (RR 0.7, 95% CI 0.4-1.1, p = 0.13). A family history of FS, a family history of epilepsy, the gender and age of the child and the type of initial FS were included in the risk factor analysis but their influence on the recurrence rate was insignificant. The univariate risk factor analysis and the multivariate Cox proportional Hazard model gave similar results.

Assessment of the effect of recurrences on the short-term outcome showed six of the 156 patients to have developed defects in speech, seven abnormal findings in motor function tests and seven disturbances in eye movements and vision. Sixteen children had either spikes or spikes and waves in their EEG recording. No statistically significant effect of recurrences on these variables was found.

5.2.3 Effect of acetaminophen and low dose diazepam on recurrences

The prophylactic treatment trial showed acetaminophen, low intermittent doses of diazepam and their combination to be ineffective for preventing recurrences of FS as compared with a placebo.

Of the 79 children assigned to receive acetaminophen during the next febrile episode, eight experienced a FS recurrence during that episode, whereas seven recurrences were recorded among the 74 children in the placebo group (Table 3).
Table 3. Numbers of patients and recurrences of FS during the next fever episode after the initial FS, by mode of treatment.

<table>
<thead>
<tr>
<th>Treatment during next fever episode</th>
<th>No. of patients in treatment group</th>
<th>No. of recurrences (%) during next fever episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam + Placebo</td>
<td>35</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Placebo + Acetaminophen</td>
<td>40</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>Diazepam + Acetaminophen</td>
<td>39</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Placebo + Placebo</td>
<td>39</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>All treatment groups</td>
<td>153</td>
<td>15 (9.8)</td>
</tr>
</tbody>
</table>

The differences in recurrence rates during the next fever episode between the children assigned to diazepam, acetaminophen or both and those receiving only placebo treatment were not statistically significant.

There were altogether 23 FS recurrences during 314 acetaminophen-treated fever episodes during the 2-year follow-up (7.5%) and 32 recurrences during 327 placebo-treated fever episodes (9.8%) (Table 4). Thus acetaminophen had no effect on recurrences of FS.

Table 4. Numbers of fever episodes and recurrences during the 2-year follow-up by mode of treatment.

<table>
<thead>
<tr>
<th>Treatment during fever episodes</th>
<th>No. of fever episodes</th>
<th>No. of recurrences (%) during fever episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam + Placebo</td>
<td>156</td>
<td>18 (11.5)</td>
</tr>
<tr>
<td>Placebo + Acetaminophen</td>
<td>173</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>Diazepam + Acetaminophen</td>
<td>141</td>
<td>14 (9.9)</td>
</tr>
<tr>
<td>Placebo + Placebo</td>
<td>171</td>
<td>14 (8.2)</td>
</tr>
<tr>
<td>All treatment groups</td>
<td>641</td>
<td>55 (8.6)</td>
</tr>
</tbody>
</table>

The differences in recurrence rates during the fever episodes between the patients assigned to diazepam, acetaminophen or both and those assigned to placebo treatment were not statistically significant.

Parents gave similar amounts of extra antipyretic agents to the children receiving acetaminophen as to those receiving placebo treatment. The mean temperature during each febrile episode was 0.5°C higher in those children who had seizures than among those who did not, but the mean difference in the highest temperatures for all febrile episodes between the acetaminophen and placebo groups was not significant (difference 0.3°C, p >0.05). Even though acetaminophen reduced the mean temperatures, it had no effect on the highest temperatures or on the temperatures in those patients who had FSs.

Of the 153 patients experiencing febrile events during the 2-year follow-up, 74 had been assigned to receive diazepam and 79 to receive placebo treatment during all subsequent fever episodes. The numbers of patients with at least one recurrence during follow-up in these groups were 21 (28.4%) and 17 (21.5%), respectively. No statistically significant difference in the recurrence rates could be found between these groups, nor did the Kaplan-Meier method show any difference in the timing of the first recurrence (Fig 2).
Fig. 2. Cumulative incidence of recurrent FS, by anticonvulsive treatment group
(–––Diazepam, ---- Placebo). The difference between the curves was not significant (P=0.4138).

Similarly, no difference in recurrence rates was observed between the diazepam and
placebo groups during the next fever episode (Table 3) or any subsequent episode
(considered in rank order).

The combination of antipyretic and anticonvulsive medication did not reduce the
recurrences of FS compared with any other treatment regimen used (Table 4).

5.3 Meta-analysis of preventive treatment for febrile seizure recurrences

Of the nine articles accepted in the meta-analysis, four evaluated the effect of continuous
phenobarbital on recurrences of FS in a placebo-controlled setting (Camfield et al. 1980,
Bacon et al. 1981, Mamelle et al. 1984, Farwell et al. 1990), one of them also evaluating
the prophylactic effect of valproate (Mamelle et al. 1984) and another phenytoin (Bacon
et al. 1981). One paper compared the effect of intermittent phenobarbital with placebo
treatment (Mackintosh 1970), three evaluated the prophylactic effect of diazepam (Autret
et al. 1990, Rosman et al. 1993, IV) and one considered the effect of pyridoxine on
recurrences (McKiernan et al. 1981). The test of heterogeneity applied to the data
concerning each treatment showed this to be insignificant, justifying the combination of
the material.

The meta-analysis revealed a significant reduction in the FS recurrence rate in children
receiving continuous phenobarbital relative to placebo treatment (OR 0.54, 95% CI 0.33-
0.90, p = 0.017), whereas the only assessment of intermittent phenobarbital treatment
relative to a placebo showed no difference in the risk of recurrence between the groups (OR 0.51, 95% CI 0.10-2.62, p = 0.41). The combined results of the three trials evaluating the effect of diazepam administered during fever episodes showed no effect of this intermittent treatment on the FS recurrence rate relative to a placebo (OR 0.81, 95% CI 0.54-1.22, p = 0.31). The one comparison of continuous valproate with a placebo showed a preventive effect on further recurrences (OR 0.09, 95% CI 0.01-0.78, p = 0.011). Both pyridoxine and phenytoin were ineffective when compared with a placebo.

The number of patients that it was necessary to treat in order to avoid one recurrence of FS was eight for phenobarbital and four for valproate. For the drugs with insignificant efficacy in the meta-analysis, 26 patients would have had to be treated with intermittent diazepam, 119 with phenytoin, and 16 with pyridoxine to prevent one recurrence.

### 5.4 Results of the mesial temporal sclerosis survey

The results of the evaluation of the causal relation between FS and MTS were negative. The qualitative examinations of the mesial temporal area by MRI revealed no cases with sclerosis, and there were no statistically significant differences in absolute right or left hippocampal formation or amygdala volumes between either the patients with a prolonged initial FS or those with an unprovoked seizure after the initial FS and those with a single simple FS. The mean right-left hippocampal volume difference was significantly smaller in the patients with a prolonged initial FS, i.e. 0.039 cm$^3$ than in the controls, 0.18 cm$^3$ (p <0.01) (Table 5), and the eight cases with a focal prolonged initial FS had an even lower mean difference, -0.081 cm$^3$ vs. 0.18 cm$^3$ (p <0.001).

#### Table 5. Results of MRI volumetry. Mean (SD) structural volumes, in cm$^3$, for the children with initial prolonged or simple FS and those with later unprovoked seizures.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unprovoked seizure after FS (n=8)</th>
<th>Prolonged initial FS (n=24)</th>
<th>Single simple FS (n=32)</th>
<th>P-value of differences between the groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right HF</td>
<td>2.95 (0.27)</td>
<td>2.83 (0.42)</td>
<td>2.98 (0.40)</td>
<td>0.34</td>
</tr>
<tr>
<td>Left HF</td>
<td>2.83 (0.30)</td>
<td>2.79 (0.42)</td>
<td>2.80 (0.36)</td>
<td>0.96</td>
</tr>
<tr>
<td>Right-left difference in HFs</td>
<td>0.12 (0.16)</td>
<td>0.039 (0.19)</td>
<td>0.18 (0.16)</td>
<td>0.012*</td>
</tr>
<tr>
<td>Right amygdala</td>
<td>2.03 (0.28)</td>
<td>2.04 (0.24)</td>
<td>2.06 (0.30)</td>
<td>0.97</td>
</tr>
<tr>
<td>Left amygdala</td>
<td>1.99 (0.26)</td>
<td>2.01 (0.26)</td>
<td>1.95 (0.28)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

HF, hippocampal formation. *Significant differences between patients with prolonged initial FS and the control group in Bonferroni multiple comparison: mean difference = -0.1411, 95% CI 0.254--0.028, p-value <0.01.

Five children in the prolonged FS group had an initial attack lasting 60 minutes and one child 150 minutes, but their mean volume and volume difference values did not differ from those of the patients with a prolonged seizure lasting from 30 to 59 minutes. The longest duration of a focal prolonged initial seizure was 60 minutes, observed in one child. The mean hippocampal volume difference in the patients with an unprovoked seizure was similar to that for the controls. The results of the comparison between the
mean greater-smaller hippocampal volume differences for the groups were similar to those of the analysis in terms of the mean right-left hippocampal volume difference.

According to our threshold values for the right-left hippocampal volume difference (relative to the values for our controls), three patients in the prolonged FS group had a smaller right hippocampal formation (right-left volume difference ranging from -0.47 cm$^3$ to -0.15 cm$^3$), while one left-handed control had a volume difference of 0.52 cm$^3$. All these four patients were neurologically normal, without unprovoked seizures.

The school performance and neurological findings of the patients with a prolonged initial FS were as good as those of the control group. The children with problems in school performance or abnormal neurological findings had similar hippocampal formation and amygdala volumes and right-left volume difference in hippocampal formations to the patients with normal neurological status and no problems in school performance. Three patients with a prolonged initial FS, three with a later unprovoked seizure and eight controls had mild abnormalities in the motor function tests, and three patients in the prolonged FS group, two in the unprovoked seizure group and one control had a history of problems in school performance. There were no statistically significant differences in school performance between the patients with a prolonged primary FS, those with a later unprovoked seizure and the controls.

The mean absolute hippocampal and amygdala volumes and the right-left volume differences in the patients with multiple first seizures (three cases) and those with up to ten recurrences during the two-year follow-up (four cases) were similar to the values for the control patients.
6 Discussion

6.1 Study design

This work was originally started with a randomized, placebo-controlled trial evaluating the effect of diazepam and acetaminophen on recurrences of FS (IV). As this regimen lacked any effect in our trial (IV), a need arose for a further analysis of risk factors for recurrences, especially factors that were amenable to intervention (II). Since at that time no consensus had been reached on the prevention of recurrences, a meta-analysis of the literature on medical prophylaxis against recurrences was conducted (III). The possible role of PGs in FS pathogenesis needs further consideration, as PG synthetase inhibitors are widely used as forms of antipyretic treatment for children. To start with, we performed a systematic review on this subject (I). Although FS are considered benign, a causal relation with MTS has been suggested. The FS patients that we used for the outcome analysis with respect to MTS (V), was a representative sample of cases followed up prospectively for more than a decade.

6.2 Prostaglandins and their synthetase inhibitors in relation to febrile seizures

Our systematic review suggested that some endogenous PGs produced in the brain (PGD2, PGE1, PGE2) provide protection from seizures in animals, while others (notably PGF2alfa) have mainly aggravating effects (Table I). PGF2alfa and PGE2 have been used for the induction of abortion and labour in women, but seizures have been reported in only one series, where five out of 320 patients (including two with a history of epilepsy) had seizures after intra-amniotic administration of PGF2alfa (Lyneham et al. 1973). A causal relationship between PGF2alfa or PGE2 infusion and seizures in normal individuals is therefore unlikely.

Non-steroidal anti-inflammatory agents (NSAIDs) inhibit the multi-enzyme complex COX and thus reduce PG synthesis. In our review diclofenac, fluriprofen and indometacin, which are strong inhibitors of the COX enzymes, mainly increased seizure
susceptibility, while ibuprofen, mefenamic acid, meclofenamic acid, acetaminophen and sulindac, possessing a weaker COX inhibition capacity, had an inhibitory effect on most seizures induced chemically (with PTZ, flurothyl or penicillin), but no effect on those induced electrically. Acetylsalicylate was an exception to this, provoking seizures even though it is a weak COX inhibitor (Climax & Sewell 1981). The anticonvulsive effect of the weak COX inhibitors (except acetylsalicylate) increased in a dose-dependent manner, but the strong COX inhibitors all provoked seizures. Thus the intensity of COX inhibition does not fully explain the seizure susceptibility modulating effect of NSAIDs.

The PG synthetase inhibitors vary in structure and differ not only in the intensity of their inhibition of COX enzymes but also in their COX-1 and COX-2 enzyme inhibition ratio (Vane et al. 1996), which may explain their effect on seizure susceptibility. The role of COX-2 activity in kainic acid-induced seizures in mice was evaluated by Baik et al. (1999), who found that selective inhibitors of this activity attenuated PG production and increased neuronal death in the hippocampal formation most profoundly. The aggravating effect of unselective PG synthetase inhibitors on seizures was related to their COX-2 inhibition intensity. These findings indicate a need for further studies of the possible seizure inhibiting and neuroprotective effects of COX-2 activity and also offer a possible explanation for the effects of different COX inhibitors in relation to their COX-1 and COX-2 inhibition intensity.

Elevated levels of PGF2alpha and PGE2 are found in the CSF of children after a FS (Tamai et al. 1983, Löscher & Siemes 1988). NSAIDs inhibit PG synthesis and are effective antipyretic drugs, but their effect on seizures is not clear. If NSAIDs reduce fever by inhibiting the synthesis of anticonvulsive PGs, the net effect on the risk of FS is unpredictable. Acetaminophen in our treatment trial (IV) and ibuprofen in that of van Stuijvenberg et al. (1998) were ineffective in preventing FSs, and similarly neither acetaminophen nor ibuprofen prevented PTZ induced seizures at low doses in animal models and electrically (MES), bicuculline or flurothyl-induced seizures at any dose (Table 2). These findings imply that the pathogenesis of FS in children may bear similarities to these artificially induced seizures in animals. It is notable, however, that there are no studies on immature animals in this field, as all the experimental work in our systematic review had been performed with adult animals. On the other hand, FSs only occur in children, and epileptogenesis differs between the adult and immature brain. Since it is possible that PGs and their synthetase inhibitors act differently in immature animals, no direct conclusions about the effects of PGs and their synthetase inhibitors on seizure susceptibility in humans can be drawn from these publications.

The diversity of methods used for the induction of seizures in experimental animal models in the review also made the comparison of the results and interpretation of the data difficult. As FSs are usually generalized tonic-clonic seizures and MES-induced seizures are considered a prototype model for these (Fisher 1993), MES-induced seizures offer the most suitable model for FS among those mentioned in the review. MES has not been used in experimental FS studies, where seizures have been induced by various applications of external heat (Millichap 1959, Chen et al. 1999), but these models do not optimally mimic FS in humans.
6.3 Opportunities to modify risk factors for recurrences

The results of our risk factor survey corroborate previous findings in which frequent fever episodes after the initial FS markedly increased the risk of recurrences (Knudsren 1988, Rantala & Uhari 1994). In our material, each fever episode after the initial seizure increased the recurrence risk by 18% (p = 0.0003). The quantitative effect of febrile episodes on recurrences has not previously been evaluated. High fever is the strongest factor triggering the first FS (Rantala et al. 1995, Berg et al. 1995), and each degree of rise in body temperature during subsequent fever episodes almost doubled the risk of recurrence in the current trial (RR 1.9, p = 0.043).

Young age at the onset of FSs was found to increase the recurrence risk in 12 out of the 14 reports evaluated by Berg et al. (1992) in their meta-analysis. We did not find, however, that age reached statistical significance as a predictor of recurrences, perhaps partly because of the collinearity between age and the number of subsequent fever episodes. The height of the temperature during the initial FS had a low risk ratio (RR 0.7) in our data, but its effect on the frequency of recurrences was not statistically significant (p = 0.13). The lack of a decrease in the risk of recurrences in association with high temperature may well be due to the small sample size in our material. Several other studies have found a significant reduction in recurrences in children with high fever during initial FS (Berg et al. 1992, El-Radhi & Banajeh 1989, Offringa et al. 1992).

Efforts to prevent febrile infections by restricting the number of infectious contacts might theoretically reduce the risk of recurrence. The most effective way to restrict the number of infections in children would be to avoid large day-care centres or nursery groups. Interventions to prevent the spread of infective agents in day-care centres have also been shown to reduce infections (Uhari & Möttönen 1999). Whether child-care at home could prevent children with a history of FS from suffering further recurrences better than outside day-care is not known. Nevertheless, the fear of multiple or complicated recurrences, and parental anxiety in general, could lead to interventions in the type of day-care.

6.4 Antipyretic drugs for preventing recurrences

As high fever is the major triggering factor for FS (Rantala et al. 1995, Berg et al. 1995) and antipyretic drugs acting via the PG system are widely used in children, the effect of antipyretics on recurrences of FS should be evaluated. Although high amounts of PGs occur in the CSF of children after FS relative to children with unprovoked seizures (Tamai et al. 1983), ibuprofen and acetaminophen seem not to prevent recurrences (van Stuijvenberg et al. 1998, IV). The low dose of acetaminophen used in our trial (40 mg/kg/24h) does not explain the negative finding. Acetaminophen did not lower the mean body temperature during the fever episodes associated with a FS recurrence, although it was antipyretic in episodes without seizures (IV). Similarly no antipyretic effect of ibuprofen during fever episodes with seizures was observed by van Stuijvenberg et al. (1998). Likewise Schneiderman et al. (1993) reported a lack of antipyretic effect in the case of higher doses of acetaminophen (90-120 mg/kg/24h) among children hospitalized for FS.
Our systematic review of PGs and their synthetase inhibitors showed that NSAIDs in adult animals did not inhibit MES-induced seizures, which are a prototype model for generalized tonic-clonic seizures (Fisher 1993) and thus the best of the current animal models for FS (I). This finding supports the assumption that NSAIDs might not have any prophylactic effect on FS at any dose, although no direct conclusions concerning FS can be drawn from animal studies (I).

The clinical failure of PG synthetase inhibitors to prevent recurrences is interesting. It suggests that either PGs are not important in the pathogenesis of FS or the diversity of inhibition mechanisms in PG synthesis nullifies the effect. If this is the case, trials using different types of NSAIDs are urgently warranted, as they could lead to the development of selective NSAID preparations capable of improving seizure inhibition and neuroprotection.

Even though acetaminophen, a weak inhibitor of PG synthesis, does not seem to prevent FS, it is unlikely to counteract the synthesis of seizure-inhibiting PGs. Thus it may be the most suitable antipyretic medication for children with FS.

### 6.5 Anticonvulsant treatment for preventing recurrences

Both phenobarbital and valproate were effective in preventing recurrences in our meta-analysis, but these drugs are not recommended for FS patients on account of their side-effects (Committee on Drugs 1982, Farwell et al. 1990).

The use of intermittent diazepam has been advocated since the observation by Knudsen and Vestermark (1978) that the effect of intermittent diazepam suppositories on recurrences was similar to that of continuous phenobarbital treatment. The meta-analysis nevertheless found only three placebo-controlled trials evaluating the effect of intermittent diazepam. In our treatment trial, diazepam administered during fever did not prevent recurrences in unselected FS patients (IV). The low dosage of diazepam used may have contributed to this negative result, but the same dose has previously been reported to be effective in preventing recurrences (Knudsen 1985). Rosman et al. (1993) showed a higher dose of diazepam (0.33 mg/kg every eight hours) to have a prophylactic effect in children with an increased risk of recurrences in a placebo-controlled setting, the intention-to-treat analysis revealing a relative risk of 0.56 (95% CI 0.38-0.81, p = 0.002) for recurrences in children assigned to diazepam compared with the placebo group. The effectiveness of diazepam in this case may have been due to the dose, but also to patient selection, as about a half of the patients were participating in the trial after their first recurrence. The third placebo-controlled trial led to the conclusion that diazepam had no effect on recurrences (Autret et al. 1990). Our meta-analysis combining all the available data shows that intermittent use of diazepam appears to be ineffective for preventing FS recurrences.

If diazepam is recommended as prophylaxis for FS, the dose should be 0.33 mg/kg every eight hours while fever last. Its side-effects at high doses can make the follow-up of a feverish child difficult and also cause problems with compliance. As the prognosis for FS is benign (Knudsen et al. 1996), the use of intermittent diazepam should be carefully considered.
6.6 Febrile seizures and mesial temporal sclerosis

Our finding that patients with different forms of FS had no signs of MTS indicates that its occurrence after a FS is an uncommon event. Due to the relatively small sample of children with very prolonged FSs, their role as a risk factor for MTS could not be excluded with certainty.

An average right-left absolute hippocampal volume difference of 0.2 cm³ has been reported in healthy adults (Jack et al. 1990). Using standard deviations from this series, lower and upper threshold values of –0.2 cm³ and 0.6 cm³ were calculated and then used to classify the patients into groups with right-sided hippocampal atrophy, nonlateralizing volume difference and left-sided hippocampal atrophy (Jack et al. 1992). Since there are no normal values for adolescent patients, we used the findings in our control group, i.e. patients with a single simple FS, as a source for reference values. Our finding of a mean right-left hippocampal volume difference of 0.18 cm³ is quite close to the above value of 0.2 cm³ reported for adults. The right-left hippocampal volume difference threshold values in our adolescent control patient group (2 SD range) were –0.13 cm³ and 0.49 cm³.

Our results demonstrate a significantly smaller hippocampal right–left volume difference, without any decrease in mean absolute hippocampal volumes, among the patients with a prolonged initial FS than among the matched controls. Right-left volume asymmetry in patients with severe TLE and unilateral hippocampal sclerosis has previously been linked to hippocampal atrophy (Kuks et al. 1993, Free et al. 1996), but we could not find this in our patients. Perhaps there are subtle forms of MTS that cannot be detected with MRI, although this has been considered to be the most sensitive non-invasive method for evaluating moderate and severe MTS (Jack et al. 1992). Only further follow-up of the patients can reveal whether the cases of hippocampal volume asymmetry without signs of absolute volume reduction and structural damage will develop into unilateral hippocampal atrophy. Our present follow-up period was nevertheless a long one, so that if changes were to develop as a consequence of FS the findings should have been in evidence by now.

Conclusions concerning the outcome of FS cannot be derived from highly selected TLE patient series, for in cases of severe TLE the fever may have been the first trigger leading to the seizures and the structural changes in the mesial temporal area may well have been there earlier (Fernandez et al. 1998).

MTS is found in only about one per cent of children with newly diagnosed epilepsy (King et al. 1998, Berg et al. 2000), but its occurrence in children with FS has not previously been evaluated. We collected a population-based series of patients and followed them up prospectively from the first FS, selecting the ones most likely to have an adverse sequel, i.e. those with a prolonged initial FS or unprovoked recurrences. It is not probable that new cases with epilepsy will turn up later among these FS patients, because of the long follow-up period. If epilepsy arises, usually it occurs within nine years of the FS (Annegers et al. 1979), and our follow-up time was over 12 years. Although the sample size was relatively small, our results support the conclusion that there is no causal relation between FSs and MTS in an unselected series of FS patients.
7 Conclusions

Elevated amounts of PGE2 and PGF2alfa occur in the CSF after a FS. Our systematic review demonstrated that different endogenous PGs have seizure-modulating effects ranging from inhibition (PGD2, PGE1 and PGE2) to provocation (PGF2alfa) in animals (I). Thus the PG system is probably important in the pathogenesis of FS.

High fever and frequent fever episodes are powerful risk factors for recurrences (II). Efforts to prevent frequent febrile infections by restricting the number of infectious contacts, e.g. by rearranging day-care, might reduce the risk of recurrence, but this theory has not yet been proved.

Acetaminophen did not have an antipyretic effect during fever episodes with recurrences, and it did not prevent FS in our treatment trial (IV). There is no evidence that FS recurrences could be prevented with antipyretic medication. PG synthetase inhibitors (NSAIDs) attenuate fever, but as they modulate the PG balance in the brain, they could simultaneously alter seizure susceptibility. The seizure-modulating effects of NSAIDs were evident in our review, but diverse results had been obtained in experimental models involving adult animals. These findings have not been confirmed in humans (I).

Low intermittent doses of diazepam did not reduce recurrences of FS in our treatment trial (IV). Similarly, our meta-analysis of prophylactic treatment against FS revealed the ineffectiveness of diazepam for preventing recurrences (III). Even though both continuous phenobarbital and valproate have been shown to reduce recurrences, their use is not acceptable on account of their severe side-effects. Thus there is no safe and effective medication available for the prevention of FS.

We found no MTS in our prospectively followed FS patients (V). Its occurrence, even following a prolonged FS, must be an uncommon event, confirming the good clinical outcome of FS.
8 References


Verity CM, Butler NR & Golding J (1985b) Febrile convulsions in a national cohort followed up from birth. II – Medical history and intellectual ability at 5 years. BMJ 290: 1311-1315.


