Diagnosis and Prognosis of Seizures and Epilepsy in Childhood

(Dutch study of epilepsy in childhood)

Diagnose en prognose van epileptische aanvallen en epilepsie op de kinderleeftijd

(Dutch study of epilepsy in childhood)

Hans Stroink

Cover: “In the shade of awareness...”
painted by Hans Innemée for this thesis, 2008, design Peter de Jong.

Toelichting schilderij “In the shade of awareness...” door Hans Innemée.

Aanwezigheid, afwezigheid zijn in mijn beleving relatieve begrippen. Tijdens epileptische aanvallen is mijn zoon Martijn even niet meer bewust in het hier en nu, althans voor hem zelf niet.
Voor mij als vader des te meer, ik beleef zijn “even weg zijn” met een intens bewustzijn.
De wereld gaat “even op zijn kop”. Het beeld van de vogel als heldere tekening tussen de donkere banen waarin het negatief van de tekening van de vogel is verwerkt verbeeldt “To be AND not to be...”(vrij naar Shakespeare) maar dan in één beeld, in één tijd, tegelijkertijd.

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Promotor:

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Overige leden:

Prof.dr. A.P. Aldenkamp

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Prof.dr. P.A. Sillevis Smit

Copromotor:

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Chapter 1

General introduction

Introduction

Many people suffer from one or more epileptic seizures during life, but not all these people have epilepsy. Moreover, epilepsy is not one disease or syndrome, but a collection of different disorders, which have in common the *repeated* occurrence of *unprovoked* epileptic seizures during some time in life.[1-3] There are many genetically determined and acquired causes of epilepsy. The symptomatology of the seizures can be very different.[2 3] Also the course in time of epilepsies is very diverging. The cause, symptoms, signs and course are influenced to a great deal by age. Therefore, the epilepsies in childhood and in adulthood differ in many aspects.[1 3] For this reason, children and adults should not be mixed in studies on epilepsy.

A recent population based study in Denmark found an incidence of 83 new epilepsy patients per 100,000 person-years at risk. The prevalence of active epilepsy was 0.6% with the highest prevalence in childhood and the lowest between 20 and 40 years.[4] In 70% of patients epilepsy starts before the age of 20 years with the highest incidence in young children.[5] In the Danish study the incidence in the first year of life was 200 per 100,000 children. The cumulative incidence of a period of active epilepsy was 1% at the age of 10 years and 2% at the age of 25 years.[4] So epilepsies are more common in childhood.

Many studies on the cause and prognosis of epilepsy are done in specialised epilepsy centres. This may cause a bias to more severely affected patients. Moreover little is known of the natural history of epilepsy because almost all patients are treated with anti-epileptic drugs (AEDs). Many children are still treated even after a single seizure.[6]

"Het Zuid-Hollands Kinderepilepsie Onderzoek" (ZHKO) started in1988. The ZHKO was initiated by the paediatric neurologists Willem Frans Arts, Boudewijn Peters, Oebo Brouwer and Hans Stroink (at the time they were employed at the Westeinde Hospital and Juliana Children's Hospital in The Hague, and at the university hospitals of Leiden and Rotterdam), by the neurologist Cees van Donselaar and by the epidemiologist Ada Geerts (Rotterdam). Due to the move of participating paediatric neurologists to other hospitals, later on the departments of paediatric neurology of the University Hospitals of Groningen and Utrecht, and the departments of paediatric neurology of the St. Elisabeth Hospital and TweeSteden Hospital in Tilburg joined, whereas the University Hospital of Leiden left the study group. In 1998 "Het Zuid-Hollands Kinderepilepsie Onderzoek" was renamed "Dutch Study of Epilepsy in Childhood" (DSEC).

To prevent the bias mentioned before, we created a cohort of unselected children

by enrolling consecutively all children aged one month through 15 years with new onset epilepsy referred to the participating hospitals from August 1, 1988, to August 1, 1992. The intake of children with a single unprovoked seizure started somewhat earlier on January 1, 1988. Children treated before with AEDs and children referred from other hospitals were excluded, again to prevent bias to more severely affected patients.[7-10] The object was to study many aspects of childhood epilepsy in this cohort with unselected children, as reliability and accuracy of the diagnosis, prognosis, comorbidity, quality of life, and cognitive and behavioural disturbances. The attending paediatric neurologist completed extensive questionnaires on the description of the events including postictal signs, possible provoking factors, previous medical history and family history. We performed a standard electroencephalogram (EEG) in each child. If this did not show epileptiform discharges, a recording after partial sleep deprivation was made, or in the case of very young children, during a daytime nap. In the first years of the study in most children a CT scan of the brain was performed, later on in most children a MRI scan. All recruited children were discussed before inclusion by a panel consisting of three out of the four participating paediatric neurologists in an attempt to make the possibility of a misdiagnosis of epilepsy as low as possible and to prevent exclusion of children due to an unjustified diagnosis of a non-epileptic paroxysmal event. They also classified the type of seizure and the epilepsy syndrome.[1 2 7-10] To prevent bias, none of the paediatric neurologists was allowed to judge his own patients, but only those who were seen by one of the other panel members. The panel included 760 children for follow-up: 170 with a single seizure, 412 children with epilepsy according to the judgment of the panel; 54 children had one and 124 children multiple paroxysmal events without a clear diagnosis; 121 children were excluded because the events were diagnosed as non-epileptic.[8] The cohort comprised about 75% of the expected incidence of childhood epilepsy in the referral areas of the participating hospitals.[10] So a rather unique cohort of children, who were not treated before with AEDs, with single unprovoked epileptic seizures and new onset epilepsy was obtained. Children with single unprovoked seizures were followed initially for at least two years and children diagnosed with epilepsy for five years. Children with one or more unclear events (including children with presumed pseudo-seizures) were followed for one year to assess whether new episodes might yield firm evidence for a definite diagnosis. An unclear event was defined as a paroxysmal event not considered as an epileptic seizure, but without another obvious explanation. Later on the follow-up of children with epilepsy was extended to a median of 14.8 years. Children with a single unprovoked seizure and children with unclear events were not treated with AEDs. In children diagnosed

with epilepsy, the decision whether or not to treat the child with AEDs was made by the child's paediatric neurologist. The paediatric neurologist was free in selecting and dosing AED(s). Many of the investigated aspects of childhood epilepsy in this cohort have been published by various authors, such as cognition and behaviour[11-14], quality of life[15-17], diagnostic yield of a second EEG after partial sleep deprivation[18], the relation between the duration of treatment with AEDs and the recurrence rate after withdrawal[19 20], prediction of intractability and good outcome early in the course of epilepsy[9 10 21], mortality[22], familial occurrence of epilepsy[23] and immunology of childhood epilepsy.[24] A complete list of papers is found in this book in the publication list of the DSEC.

In this thesis, several topics concerning the diagnosis and the prognosis of single seizures and epilepsy in childhood will be discussed: reliability and accuracy of the diagnoses seizure and epilepsy; the interobserver reliability of the EEG interpretation; short-term and long-term prognosis of children with a single seizure and of children with status epilepticus.

Diagnosis

The diagnoses seizure and epilepsy may be difficult in many cases. The diagnosis depends on the description of the event by an eyewitness and the interpretation of the description by the physician.[25] Most studies on prognosis and treatment of seizure(s) do not mention the problem of making the right diagnosis at the time of inclusion. Nor does it become clear in how many patients during follow-up the diagnosis proved to be wrong.[26-28] An exception is one study in adults with a single seizure (chapter 2).[28]

For these reasons we studied the reliability and accuracy of the diagnosis seizure(s) and the reliability of the EEG interpretation in (a part of) our cohort. To study the reliability of the diagnosis of a single seizure several experienced paediatric neurologists had to diagnose one paroxysmal event of 100 children. The written description of the event was presented to them. If they concluded that the child suffered a seizure they had to classify the type of the seizure according to the ILAE classification (chapter 3).[2 29]

As mentioned above, children with the diagnosis epilepsy were followed for five years, whereas children with a single seizure initially for two years. To study the accuracy after each new event during follow-up the patient was re-evaluated. The diagnosis was also reassessed for all children diagnosed with a single seizure or epilepsy after two years follow-up. Children with an unclear event were followed

for one year to reassess whether new episodes might yield firm evidence for a definite diagnosis (chapter 4).[7 8]

The electroencephalogram (EEG) is an important tool in the diagnostic process in children suspected to have epilepsy. In most cases, the results of the EEG solely are not appropriate to confirm or refute the diagnosis of epilepsy in childhood. However, in a few syndromes like childhood absences and West syndrome the correlation is 100%. EEG findings are mainly used for the classification of epileptic seizures and syndromes, in combination with the information from the history, physical examination and possibly other additional investigations. The EEG may also aid in the choice of the appropriate AEDs. The presence of epileptiform discharges is also used to predict the risk of recurrence after a single seizure, although the recurrence rates are rather diverging in studies published before.[30-44] The reliability and accuracy determine the value of a diagnostic or prognostic tool. Data on the reliability of the visual interpretation of EEG-findings are scarce, however.[45-50] We examined the interobserver reliability of the visual interpretation of the EEG in children with new-onset epilepsy (chapter 5).[51-53]

Prognosis

The DSEC started with the inclusion of children with a single unprovoked seizure several months earlier than with the inclusion of the other children. Other studies on single seizures were published before[30-44] and of course also after our study.[6 54-63] In earlier studies differences in the way children were included and followed may explain the large variation of the recurrence rate: 23-71% after three years of follow-up. The criteria for the diagnosis seizure were never mentioned. So information on accuracy of the diagnosis is missing. In several studies children and adults were included without analysing the data separately. The interval between the seizure and the inclusion in studies is often not mentioned. This interval is of great importance because if recurrences do occur they mostly do so soon after the first seizure. Also in all studies a minority or even a majority of children were treated with AEDs after a single seizure. In our own study methods were adapted to adjust for these shortcomings (chapter 6).[7]

Status epilepticus is defined in most studies as seizures lasting 30 minutes or longer, although this duration is discussed in recent years.[64 65] When the DSEC started, information on the long term prognosis of unprovoked status epilepticus was almost completely lacking. We investigated the incidence, causes and short- and long-term outcome of status epilepticus in our cohort of children.[66] We used

the definition of seizures lasting at least 30 minutes. After the DSEC started a few other studies have been published on this subject, which also used this definition (chapter 7).[67-70]

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Part I
Diagnosis

Chapter 2

How confident are we of the diagnosis of epilepsy?

van Donselaar CA, Stroink H, Arts WF
Epilepsia 2006;47 Suppl 1:9-13

Abstract

The diagnosis of a first seizure or epilepsy may be subject to interobserver variation and inaccuracy with possibly far-reaching consequences for the patients involved. We reviewed the current literature.

Studies on the interobserver variation of the diagnosis of a first seizure show that such a diagnosis is subject to considerable interobserver disagreement. Interpretation of the electroencephalogram (EEG) findings is also subject to interobserver disagreement and is influenced by the threshold of the reader to classify EEG findings as epileptiform. The accuracy of the diagnosis of epilepsy varies from a misdiagnosis rate of 5% in a prospective childhood epilepsy study in which the diagnosis was made by a panel of three experienced paediatric neurologists to at least 23% in a British population-based study, and may be even higher in everyday practice. The level of experience of the treating physician plays an important role. The EEG may be helpful but one should be reluctant to make a diagnosis of epilepsy mainly on the EEG findings without a reasonable clinical suspicion based on the history.

Being aware of the possible interobserver variation and inaccuracy, adopting a systematic approach to the diagnostic process, and timely referral to specialized care may be helpful to prevent the misdiagnosis of epilepsy.

Introduction

Diagnosing epilepsy is usually straightforward, but in everyday clinical practice often doubts arise. Not everyone who faints with myoclonic jerks has epilepsy and the differential diagnosis of "fits, faints, and funny turns" is extensive. The diagnosis of a first epileptic seizure or epilepsy has proven to be subject to error.[1-3] The mainstay of the diagnosis is a good eyewitness account of the episode(s), but this information may be not available, be incomplete, misleading, or rather vague, and may not correspond to the definition of the various epileptic seizures. The results of the additional investigations like the electroencephalogram (EEG) may be noninformative, provide information that is difficult to interpret or may seem to be contradictory to the clinical data. The level of experience of the treating physician is also important.[3 4]

For any clinical diagnosis two questions should be considered. The first is whether others agree with the diagnosis: the interobserver variability, interobserver variation, or reliability. The second question is whether the diagnosis is correct: the accuracy or validity. To prove the accuracy of a diagnosis, a gold standard is needed.

However, for most patients with epilepsy seen in everyday care, no gold standard is available. Clearly it is not possible to admit all patients for EEG-video monitoring to assess that the episodes are really epileptic seizures. An excellent response to antiepileptic drug (AED) treatment does not preclude misdiagnosis.

The diagnosis of a first seizure or epilepsy is often subjective. Patients may be misdiagnosed as suffering from epilepsy or the diagnosis of epilepsy may be missed. The consequences of a misdiagnosis may be far-reaching: psychosocial and socioeconomic problems such as driving restrictions and loss of employment may occur, the episodes may continue, an effective treatment may be withheld or patients may be treated with ineffective drugs often in high dosages or with polytherapy. If a diagnosis of epilepsy is incorrectly made in a patient with cardiac arrhythmia, the consequences may be serious, even life-threatening.[5]

This paper reviews the diagnostic process, the interobserver variation and the accuracy of the diagnosis of a first seizure or epilepsy. The paper reflects our opinion based upon the main papers on this subject and our own work in this field.

The diagnostic process

To make a diagnosis of epilepsy the patient should have had two unprovoked epileptic seizures. The definition of epilepsy is not completely clear in case of sporadic unprovoked seizures. For example, if a person has a single unprovoked seizure and then a recurrence five years later, the diagnosis of epilepsy may not be justified. If a patient with a congenital hemiplegia or previous stroke has one epileptic seizure, epilepsy will be diagnosed by many neurologists.[6]

The first question is whether the episode was an epileptic seizure or a nonepileptic event. If it was an epileptic seizure, what type of seizure?[7] Additional investigations may determine the aetiology (third step). The fourth step is using all information to classify the epilepsy syndrome.[8] Then, one can fully advise the patient and decide about starting treatment and the selection of AEDs.

This paper focuses on the first step: was it an epileptic seizure? The main problem is that we do not have validated criteria to diagnose an epileptic seizure. We have a classification scheme to categorize the seizure.[7] But which descriptive elements of the episode warrant the diagnosis of a seizure? What if the episode only mentions loss of consciousness with some myoclonic jerks and loss of urine? Syncope, for example, may be accompanied by myoclonic jerks in many patients, by other motor symptoms like head turning and oral movements or attempts to sit up, and by incontinence for urine.[9] Cardiac arrhythmias such as occur in the prolonged QT-interval syndrome, may mimic epileptic seizures.[5] Validated descriptive criteria

to distinguish between these entities are lacking. Additional investigations and especially EEG findings may be helpful, but may also be misleading. If the clinical description points to a certain seizure type or epilepsy syndrome and the EEG findings correspond, the EEG is a useful tool for the classification of the seizure type and the epilepsy syndrome. However, the EEG may be normal in a substantial proportion of patients with epilepsy and the EEG may show epileptiform abnormalities in about 1% of aircrews undergoing routine EEGs as part of the screening procedure.[10] The prevalence of epileptiform discharges in normal children is 3.5% and even higher in children with other neurological or behavioural disorders (e.g., ADHD).[11 12] Those with epileptiform abnormalities have only a slightly increased risk to develop epilepsy.[10] Misinterpreting normal EEG patterns as epileptiform abnormalities can lead to the misdiagnosis of epilepsy.[13] The EEG may show abnormalities that seem to contradict the clinical diagnosis. For example, the clinical description may point to a partial onset whereas the EEG shows generalized epileptiform abnormalities. If the diagnosis is doubtful on clinical grounds, but the EEG shows epileptiform abnormalities, one may be tempted to make a (mis) diagnosis of epilepsy. Decision rules are lacking.

Interobserver reliability

If the interobserver variation of a diagnostic process or classification scheme is poor, such a system cannot be accurate. Hence, one should improve the interobserver variation first. Unfortunately, this phase is often skipped, probably explaining the poor performance of many of these diagnostic systems or classification schemes when applied by others or used in different circumstances.

Studies on the interobserver variation of the diagnosis of an epileptic seizure or epilepsy often focus rather artificially on one aspect such as different neurologists assessing written descriptions of the episodes, reading of EEGs, evaluating neuroimaging studies, or interpreting videos of possible epileptic seizures. The results may be influenced by the way the information is presented, the instructions to the observers (make only a diagnosis if you are absolutely sure), the views and the levels of experience of the observers. Poor reliability results in these studies may not automatically point to similar poor performance in real life since the real life situation allows consideration of all available information. An eyewitness account is the mainstay of diagnosing epilepsy. The interobserver agreement of history taking has not been investigated.[14]

First seizure

The interobserver variation of the diagnosis of a first seizure has been studied

in adults and in children.[15 16] Written descriptions of the episodes were presented to (paediatric) neurologists and the interobserver agreement was assessed. The observers did not have the EEG results. Kappa statistics were used to correct the observed agreement due to chance. Interobserver agreement in adults was moderate (kappa 0.58) when the neurologists were asked to give their clinical opinion. It was substantial (kappa 0.73) if descriptive criteria were used. For example, unconsciousness without an apparent cause with incontinence of urine is not considered to be an epileptic seizure compared with unconsciousness without an apparent cause plus a tongue bite.[15] In children, the interobserver agreement was poorer: according to clinical judgment it was moderate (kappa 0.41) and improved only slightly when comparable descriptive criteria were used (kappa 0.45).[11] So, the diagnosis of first seizure is subject to considerable interobserver disagreement.

EEG

The EEG can help classify episodes as epileptic seizures but only if the eyewitness account is very suspicious of epileptic seizures. EEG interpretation is subject to interobserver disagreement. Disagreement on whether or not the EEG shows epileptiform abnormalities is substantial and is influenced by the threshold of the reader for classifying the EEG as epileptiform. Making a syndrome diagnosis will probably also vary among different readers.[17-19]

Accuracy

To actually prove that a diagnosis is correct a gold standard is needed. In 26% of the patients who were referred because of intractable epilepsy to a tertiary centre, another diagnosis was made often based upon long-term EEG-video monitoring.[20] Good clinical practice is to refer patients in case of intractability to assess whether the diagnosis of epilepsy or the classification of the epileptic syndrome is correct. Hence, these referrals cannot be considered to be a random sample of patients being cared for in nontertiary centers. Their referral to the tertiary center was correct and one may not assume beforehand that this 26% reflects the actual "misdiagnosis rate" in everyday clinical practice. Alarming however is a misdiagnosis rate of epilepsy of 23% found in a population-based study in the United Kingdom, whereas in another 12% of patients the diagnosis proved to be disputable.[21] The authors assume that their results are representative for the entire United Kingdom. Major concern was also raised in the United Kingdom after reviewing the medical records of 214 children with epilepsy from the practice of one English paediatrician.[21] Over one-third of children diagnosed as having epilepsy were thought not to have epilepsy, and below one-third was probably overtreated. Similar rates of

misdiagnosis were found among generalist paediatricians with an interest in neurology.[4 21]Not all patients can be studied with long-term EEG-video monitoring. Several other strategies have been adopted in studies on the accuracy of the diagnosis of a seizure. One approach is "wait and see" to assess whether new information will cast doubt on the initial diagnosis. If seizures do not recur with or without AEDs (i.e., no new information), then it may be assumed that the initial diagnosis of epilepsy was correct. Yet, such an assumption may be false. Another approach is to have the medical records re-evaluated by one or more experienced neurologists, but this approach is still not an objective substitute for a gold standard.

First seizure

The accuracy of the diagnosis of a first seizure in adulthood was good in a study of 165 adults with a first seizure.[22] The diagnosis was made exclusively on the account of the episodes by a panel of three neurologists. All patients were followed according to the wait and see policy. In 6% doubts about the initial diagnosis arose mainly because a cardiac arrhythmia was found during follow-up.

The Dutch Study of Epilepsy in Childhood was a prospective cohort study of children referred with a possible first seizure or epilepsy.[2 23] The diagnosis was made by three paediatric neurologists exclusively on the description of the episodes for the children with a single event. In most of the children with multiple events the diagnosis was based only on the description of the events, but in 11% the results of both the history and EEG were combined. In all children a standard EEG was recorded, followed by an EEG after partial sleep deprivation if the first EEG showed no epileptiform discharges. A diagnosis of a first seizure was made in 170 children of whom 94 had epileptiform EEG abnormalities.[2] In none of these children doubts arose about the initial diagnosis during follow-up, but only 53 of them suffered a recurrence. In 54 children, the panel classified the episode as a single uncertain event including 14 children (21%) with epileptiform EEG discharges. In four children (7%) a diagnosis of epilepsy was made during a follow-up of one year. Three of these belonged to the group of 14 with epileptiform EEG abnormalities. Thus, the diagnosis of a first seizure was probably quite accurate in these two studies in which the diagnosis was made by a panel of experienced adult and paediatric neurologists.

Epilepsy

A diagnosis of epilepsy was made by the panel in 412 children of whom 285 had epileptiform abnormalities in their EEG.[2] In 19 (5%) children there were doubts about the initial diagnosis. The diagnoses finally made were uncertain episodes

(6), pseudo-seizures (2), syncope (2), daydreaming (3) and acute symptomatic seizure, breath holding spell, hair dressers syncope, TIA (in a child with moya-moya syndrome), anxiety disorder, and alternating hemiplegia in one child each. The misdiagnosis rate was only 2% for the children in whom the EEG had shown epileptiform abnormalities and 11% in the group without epileptiform abnormalities. In 124 children, the panel decided that the nature of the events was uncertain despite epileptiform EEG abnormalities in 27 children. In seven children (6%) finally a diagnosis of epilepsy was made; one in the group with epileptiform abnormalities (4%) and six (6%) in the group without epileptiform abnormalities.

In two British series the initial diagnosis of epilepsy was re-evaluated. Misdiagnosis of epilepsy was at least 23% in a population based study and 16% in a hospital based study.[1 3] The misdiagnosis rate for neurologists (5.6%) was much lower than for nonspecialists (19.3%) in the hospital based study.[3] In a series of 684 children referred for paroxysmal disorders, the events were classified initially as an isolated seizure (51), epilepsy (83), possible epilepsy (90), or nonepileptic events (243 children).[24] All cases were reviewed at 6–30 months after the initial diagnosis by the same physician. Of the 90 children with possible epilepsy 31 were reclassified as having epilepsy (34%), none of the children diagnosed as having epilepsy was reclassified. The remarkable accuracy, in contrast to other studies, may be explained by the relatively high number of events classified initially as uncertain or by the design of the study with the same physician making the initial and the final classification. The authors advocated the use of a diagnostic category of "uncertain events" or "unclassified paroxysmal events" instead of "possible epilepsy," and to follow these children without a straightforward diagnosis to prevent an unnecessary misdiagnosis of epilepsy.

EEG

Excluding the diagnosis of epilepsy because of normal EEG findings or making a diagnosis mainly on the EEG findings may be an abuse of the EEG.[25 26] In the Dutch study, children with a diagnosis other than epilepsy were excluded. If a diagnosis of a single seizure was made in all of the remaining 224 children referred with a single event exclusively on the basis of epileptiform abnormalities on the EEG, 11 of the 108 children (9%) would have been misdiagnosed.[2] If epilepsy was diagnosed in all children with multiple events only on the basis of EEG epileptiform abnormalities, the error rate would have been 10% (31 of 312 children).[2] The EEG appears helpful to classify seizures or epilepsy syndromes but one should not base the diagnosis of a single seizure or epilepsy mainly on EEG findings if good historical data are lacking.

Discussion

How confident are we of the diagnosis epilepsy? Clearly, the diagnosis of a single seizure or epilepsy is subjective and will be subject to interobserver disagreement and inaccuracy. The misdiagnosis rate of 5% for the diagnosis of epilepsy found in our childhood study, must be considered an absolute minimum.[2] The diagnosis was made by a panel of three experienced paediatric neurologists who discussed all patients, events could be classified as uncertain and the accuracy of the diagnosis was evaluated according to the wait and see policy. If there were no recurrences, there was no reason to change the initial diagnosis. The misdiagnosis rate of at least 23% in a British population-based study may reflect general practitioners and paediatricians without special training in epilepsy playing a central role in diagnosis and treatment.[1 4 21] More specialized physicians do better. Neurologists (mistake rate 5.6%) did better than nonspecialists (mistake rate 18.9%) in another hospital-based British study.[3] So ideally, all patients suspected of having epilepsy should have an assessment by a neurologist, but this is not possible in many countries due to available resources. The diagnosis will remain uncertain for some patients even if specialists are involved. Adopting the policy of making a diagnosis of epilepsy only when the data are beyond all doubts is unrealistic and may delay effective treatment in many patients. The risk of a diagnostic error can be minimized by taking into account all available information, especially a good eyewitness account. A home video of an event may be of great value. The previous medical history may contribute. One might argue that an EEG is indicated only if the eyewitness account has led to a reasonable suspicion of seizure(s). When events are uncertain on clinical grounds, an EEG can result in misdiagnosis due to overinterpretation, the finding of nonspecific abnormalities or the presence of (nonrelevant) epileptiform discharges that can occur in patients without epilepsy.

All these elements may be subject to interobserver variation and inaccuracy. If all the information fits into a clear pattern, a diagnosis of epilepsy can be made. If not, efforts should be made to make the information as complete as possible. When there is doubt about the diagnosis of epilepsy, patients should be classified as having an uncertain diagnosis .[2 4 24] If uncertain events occur frequently, referral to a tertiary centre for a second opinion or long term EEG-video monitoring may prevent a misdiagnosis of epilepsy. When the diagnosis is uncertain, prescribing AEDs with the hope that the response will clarify the diagnosis may harm the patient because of the psychosocial and socioeconomic consequences of the diagnosis, and the possible side effects of AEDs. Moreover, other important diagnoses such as a cardiac arrhythmia may be overlooked. If a patient with diagnosed epilepsy

continues to have seizures after treatment with two AEDs it may be useful to re-evaluate the diagnosis and classification of the seizures or epilepsy syndrome and consider tertiary centre referral.

Conclusions

The diagnosis of a first epileptic seizure or epilepsy is subjective and subject to interobserver variation and inaccuracy. This cannot be prevented completely in our everyday care, but being aware of this problem, adopting a systematic, careful approach to the diagnosis, reassessment if AEDs fail, and timely referral to a tertiary centre may be helpful to prevent a misdiagnosis of epilepsy.

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Chapter 3

Interrater agreement of the diagnosis and classification of a first seizure in childhood

Stroink H, van Donselaar CA, Geerts AT, Peters AC, Brouwer OF, van Nieuwenhuizen O, de Coo RF, Geesink H, Arts WF
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Abstract

Objective: To assess the interrater agreement of the diagnosis and the classification of a first paroxysmal event in childhood.

Methods: The descriptions of 100 first paroxysmal events were submitted to two panels each consisting of three experienced paediatric neurologists. Each observer independently made a diagnosis based on clinical judgment and thereafter a diagnosis based on predefined descriptive criteria. Then, the observers discussed all patients within their panel. The agreement between the six individual observers was assessed before discussion within each panel and after that, between the two panels.

Results: Using their clinical judgement, the individual observers reached only fair to moderate agreement on the diagnosis of a first seizure (mean (SE) kappa 0.41 (0.03)). With use of defined descriptive criteria the mean (SE) kappa was 0.45 (0.03). The kappa for agreement between both panels after intra-panel discussion increased to 0.60 (0.06). The mean (SE) kappa for the seizure classification by individual observers was 0.46 (0.02) for clinical judgment and 0.57 (0.03) with use of criteria. After discussion within each panel the kappa between the panels was 0.69 (0.06). In 24 out of 51 children considered to have had a seizure, agreement was reached between the panels on a syndrome diagnosis. However, the epileptic syndromes were in most cases only broadly defined.

Conclusions: The interrater agreement on the diagnosis of a first seizure in childhood is just moderate. This phenomenon hampers the interpretation of studies on first seizures in which the diagnosis is only made by one observer. The use of a panel increased the interrater agreement considerably. This approach is recommended at least for research purposes. Classification into clinically relevant syndromes is possible only in a very small minority of children with a single seizure.

Introduction

The diagnosis and classification of a first seizure in childhood may be difficult. The differential diagnosis of a single paroxysmal event is extensive, particularly in young children. The consequences of the diagnosis of a first seizure are far reaching: it causes an emotional shock in the family and leads to restriction of activities. The subsequent classification may have consequences for the prognosis. According to the recent practice parameter, treatment with anti-epileptic drugs does not prevent the development of epilepsy, and treatment should be considered only in special circumstances.[1] Nevertheless, many children are at present still treated with

anti-epileptic drugs after a first unprovoked seizure.[2] An objective test to confirm or refute the diagnosis of first seizure is missing. Epileptiform discharges on EEG recordings are not rare in children without epilepsy,[3–5] whereas as many as 41% of patients with epilepsy and 56% of children with a first seizure have no epileptiform discharges on their standard EEG.[6,7] The very low diagnostic value of EEG in children with single events of disputable origin was shown in an earlier study.[7 8] Therefore, the diagnosis has to be based on the description of the episode given by an eyewitness, or sometimes by the child itself if he or she is old enough. For these reasons it is difficult to assess the accuracy[8 9] of the diagnosis and classification of a first paroxysmal event, and little is known about the reliability (consistency, interrater and intrarater agreement) of the diagnosis. Earlier studies on children with single seizures did not mention these diagnostic problems.[10–19] A study in adult patients showed that the use of diagnostic criteria formulated in simple descriptive terms and discussion between neurologists improved the diagnostic agreement.[20]
In a prospective hospital based multicentre study (Dutch Study of Epilepsy in Childhood, DSEC), we enrolled all children with suspected single seizures[7] or epilepsy.[21 22] We used previously defined descriptive criteria to diagnose seizures. In this part of the study under experimental conditions we evaluated the interrater agreement on the diagnosis and classification of a first paroxysmal event in childhood, and compared the results with the original diagnosis. We assessed whether the use of predefined criteria and discussion of the available data in a panel improved the interrater agreement.

Patients and methods

Two hundred and thirty three children, aged one month to 16 years, were included in the DSEC after a single unprovoked paroxysmal episode. This episode was considered as either a seizure or an unclear event by the paediatric neurologist of one of the four participating hospitals.[7] Children with a clear diagnosis other than epileptic seizure were not referred systematically. The mean age was 6.2 years, median 6.0 years (25th percentile 2.0; 75th percentile 9.0); 110 were boys. The paediatric neurologist made a description of the event, and completed an extensive questionnaire on the episode, previous medical history, and findings on physical examination. All children were discussed in the original panel of the four paediatric neurologists participating in the DSEC (HS, AP, OB, WA) to assess the diagnosis according to predefined diagnostic criteria (table 1). This list contained descriptions of all possible seizure types, but in table 2 of this paper we only mention seizures which may present as a single event. The events were classified as

epileptic seizure (170), other diagnosis (9), or unclear event (54). The study on the prognosis and prognostic determinants of these children was published in 1998.[7]
One year after the intake for children with a single event into the DSEC had been closed, two of the authors (HS, CD) selected 100 events from the diagnostic categories mentioned above. The intake panel of the DSEC considered 51 children to have had an epileptic seizure, nine an event with a clear other diagnosis (like breath holding spell or syncope), and 40 an unclear event. The number of children with an unclear event was set proportionally higher than in the original cohort of the DSEC to encourage discussion on their diagnosis and to diminish agreement due to chance. The mean age of the children was 5.6 years, median 6.0 years (25th percentile 2.0; 75th percentile 9.0); 52 were boys. Two new panels were formed. Panel A consisted of three of the four paediatric neurologists from the original panel, each with at least 10 years of experience in paediatric epilepsy and in working in such an interactive way (AP, OB, WA). Together with HS, they started the DSEC in 1988. Panel B consisted of three experienced senior paediatric neurologists at that time working in other hospitals. One (HG) was attached to an epilepsy clinic, one (ON) to a university centre for epilepsy surgery, and one (RC) to a university hospital for children. The members of both panels received anonymous descriptions of the 100 events, as given in the letter to the family physician. This included possible provoking factors and postictal signs, the previous medical history, the results of the physical examination, and an assessment of the mental development. They were distributed in random order and did not include the results of additional investigations (EEG, imaging, etc). The paediatric neurologists were not aware of the stratification policy. Firstly, each member decided independently on the question "Was it a seizure?" and, if applicable, on seizure classification according to his personal judgment. Subsequently, they independently repeated this process using the predefined descriptive criteria (table 2). Then the observers discussed all patients within their own panel until they reached consensus on the diagnosis and, if applicable, classification of the event according to the predefined descriptive criteria. Next the panels received information on the results of the EEG, imaging study, and possible other relevant information. With this new information, both panels were independently asked again to classify the seizure in an epileptic syndrome, according to the classification of the International League Against Epilepsy (ILAE), despite the single occurrence of the event.[23] The panels were forced to reach consensus in all cases.
We evaluated the interrater agreement between the individual paediatric neurologists, between both panels after discussion between their members, and between both panels and the original panel deciding on inclusion in the DSEC. As part

of the observed agreement can be attributed to chance, we used kappa statistics to assess the interrater agreement for each pair of observers and between the panels. The kappa is the ratio of the observed agreement beyond chance to the maximal potential agreement beyond chance. A kappa of 0.0 indicates that the observed agreement can be attributed completely to chance. A kappa of 1.0 means the observed agreement is maximal, a kappa of –1.0 means the observers totally disagree.[24] For intermediate values, Landis and Koch suggested the following interpretations: below 0.0, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; 0.81–1.00, almost perfect.[25] All 17 categories of the question

Table 1. Descriptive criteria for the diagnosis of a single seizure. Seizures that never will present as a single event, like absences, are not described in this table.

A. **Episode with loss of consciousness**
1. and jerks in one or more extremities or the face with or without tongue-bite (generalised seizure).
2. and stiffness in one or more extremities with or without tongue-bite (generalised seizure).
3. with only tongue-bite (generalised seizure).
4. preceded by a classical aura (generalised seizure).

B. **Episode of lowered consciousness without reaction to external stimuli**
1. staring spell without automatisms, but preceded by a classical aura (complex partial seizure).
2. episode lasting more than 30 seconds with automatisms like smacking, swallowing, blinking, grimacing, fumbling, or making continuous stereotyped movements, not remembered by the patient (complex partial seizure or absence status).

C. **Episode with normal consciousness and**
1. one-sided myoclonic jerks or stiffness in the face, jaw and/or tongue.
2. one-sided myoclonic jerks of the extremities.
3. involuntary noises from the throat.
4. paresthesias or numbness in the face, mouth, throat, tongue or extremities (one sided).
5. hypersalivation.
6. anarthria.

(1-6: simple partial seizure)

The event should not have been provoked by fever (temperature above 38^0 C, febrile seizure); pain, acute emotional upset or other known reason (collapse, blue or pale breath holding spell, Sandifer syndrome etc.), nor should it have a reasonable explanation other than epileptic.

Table 2. Questionnaires.

Diagnosis based on your own judgment

1. If you would be the attending physician, would you consider this episode to be an epileptic seizure, irrespective of the criteria presented in table 1?
   Yes/no/ unclear
2. If you answered no, your diagnosis of the event is:
3. If you answered yes, how would you classify the seizure?
   a. simple partial
   b. complex partial
   c. generalised with partial onset
   d. generalised without partial onset
   e. equivocal generalised or partial

Diagnosis with use of previously defined criteria

4. Do you think the history of the event satisfies the descriptive criteria listed in table 1?
   Yes/no/unclear
5. If you answered yes, which category is applicable? (answers one or more)?
   A1 / A2 / A3 / A4
   B1 / B2
   C1 / C2 / C3 / C4 / C5 / C6
6. Do you consider the seizure had a partial onset / partial characteristics?
   Yes/no/ unclear

Diagnosis as a panel

After your diagnosis and classification, your panel will discuss the case to reach a final common decision about the questions 4, 5, 6. After this, you will receive the results of the physical examination, EEG, imaging study and other additional investigations.

7. If your panel diagnosed the event as an epileptic seizure, the aetiology according to this panel is:
   a. idiopathic
   b. remote symptomatic
   c. acute symptomatic
   d. associated with mental retardation
   e. equivocal
8. Are you able to classify the type of epilepsy according to the ILAE classification, knowing the results of the additional investigations?

concerning seizure classification using predefined criteria were collapsed into three new categories (A1 to A4, B1 to B2, and C1 to C6; table 1). Simplification of the complex ILAE syndrome classification was reached by grouping together the categories 4, 5, and 6; 7 and 8; 9 and 10 (table 5).

Results

The kappa for pairs of individual observers for the question "Was it an epileptic seizure?" according to personal judgment varied between 0.19 and 0.60, median kappa 0.43, mean kappa 0.41 (SE 0.03). The use of the diagnostic criteria resulted in kappa values for pairs of individual observers between 0.23–0.68, median kappa 0.48, mean kappa 0.45 (0.03) (table 3).

Both panels succeeded in all cases to reach consensus on the diagnosis after discussion. The kappa between the panels was 0.60 (0.06).

The kappas for the agreement between the diagnoses made by the panels participating in this experiment and the original panel deciding on entry into the DSEC were 0.72 (SE 0.07) for the experienced panel and 0.66 (0.08) for the inexperienced panel. Conspicuously, the experimental panels agreed on the epileptic nature of the event in 61 children, whereas the paediatric neurologists deciding on entry into the DSEC considered the event to be epileptic in only 51 cases.

For seizure classification, the kappas for pairs of individual observers without use of descriptive criteria varied between 0.29 and 0.60 (median 0.46, mean 0.46, SE 0.02). The use of the predefined criteria resulted in kappas of 0.34–0.74 (median 0.62, mean 0.57, SE 0.03; table 4). The kappa between the panels after discussion within each panel was 0.69 (0.06).

Finally, after the results of the electroencephalograms and imaging study had been made available, each panel was asked to classify the epilepsy syndrome for the children diagnosed with an epileptic seizure. In 24 of the 61 children in whom both teams agreed there had been an epileptic seizure, the panels reached consensus on the syndrome diagnosis (table 5).

Table 3. Agreement (kappa) among observers concerning the question "Was it an epileptic seizure?" without (upper part table) and with (lower part) use of descriptive criteria (question 1 and question 4 of table 2). A1-3 are members of panel A, and B1-3 of panel B.

Diagnosis of a seizure with use of descriptive criteria	*Diagnosis of a seizure without use of criteria*					
	A1	**A2**	**A3**	**B1**	**B2**	**B3**
A1		0.52 (0.07)	0.43 (0.07)	0.39 (0.07)	0.31 (0.07)	0.48 (0.07)
A2	0.53 (0.07)		0.50 (0.07)	0.34 (0.08)	0.37 (0.07)	0.53 (0.07)
A3	0.47 (0.07)	0.56 (0.07)		0.25 (0.08)	0.60 (0.07)	0.60 (0.07)
B1	0.34 (0.07)	0.33 (0.07)	0.35 (0.07)		0.19 (0.08)	0.27 (0.08)
B2	0.37 (0.07)	0.48 (0.07)	0.60 (0.07)	0.23 (0.07)		0.44 (0.08)
B3	0.49 (0.07)	0.48 (0.07)	0.68 (0.07)	0.39 (0.07)	0.49 (0.07)	

Standard error (SE) shown in parentheses

Table 4. Agreement (kappa) among observers concerning the classification of the seizure type without (upper part table) and once with use of descriptive criteria (lower part) (question 3 and question 5 of table 2). Between parentheses the S.E. A1-3 are members of panel A and B1-3 of panel B.

Classification of a seizure with use of descriptive criteria	*Classification of a seizure without use of descriptive criteria*					
	A1	**A2**	**A3**	**B1**	**B2**	**B3**
A1		0.60 (0.06)	0.47 (0.06)	0.46 (0.06)	0.47 (0.06)	0.42 (0.06)
A2	0.69 (0.07)		0.58 (0.06)	0.43 (0.06)	0.51 (0.06)	0.51 (0.06)
A3	0.64 (0.07)	0.64 (0.07)		0.38 (0.07)	0.59 (0.07)	0.44 (0.06)
B1	0.40 (0.08)	0.44 (0.08)	0.40 (0.08)		0.39 (0.06)	0.29 (0.06)
B2	0.62 (0.08)	0.61 (0.07)	0.74 (0.07)	0.34 (0.07)		0.42 (0.06)
B3	0.63 (0.08)	0.69 (0.08)	0.69 (0.07)	0.42 (0.07)	0.56 (0.07)	

Standard error (SE) shown in parentheses.

Table 5. inter-panel agreement on syndrome classification.

	panel A								
panel B	No epileptic seizure	1	2	3	4, 5, 6	7, 8	9, 10	11	Total
No epileptic seizure	***25***					1		8	34
1		***4***		1					5
2			***5***						5
3	2	2		7	1			7	19
4, 5, 6	2				***5***		1	22	30
7, 8			1			***1***			2
9, 10						1		1	2
11	1							***2***	3
Total	30	6	6	8	6	3	1	40	100

Classification according to the ILAE:
1 Benign childhood epilepsy with centro-temporal spikes;
2 Other symptomatic localization-related epilepsies and syndromes;
3 Cryptogenic localization-related epilepsies and syndromes;
4 Benign myoclonic epilepsy in infants;
5 Other generalized idiopathic epilepsies not defined above;
6 Generalized idiopathic epilepsies characterized by specific modes of precipitation;
7 Other symptomatic generalized epilepsies not defined above;
8 Specific symptomatic generalized syndromes;
9 Other undetermined epilepsies not defined above;
10 Epilepsies and syndromes without unequivocal generalized or focal features;
11 Isolated seizures or isolated status epilepticus.
Agreement between both panels is indicated in the table by bold italic numbers.
Syndromes not mentioned in the table were not diagnosed.

Discussion

Our study shows that the agreement (mean kappa 0.41) between paediatric neurologists on the diagnosis of a first event as an epileptic seizure without use of criteria and without discussion is below the usual level of agreement in making a clinical diagnosis.[9,25] The agreement between the members of panel A, experienced in making a diagnosis in an interactive session using predefined criteria, was slightly but not significantly better than for panel B, whose members did not have

this experience (tables 3 and 4). Agreement could be improved only slightly by the use of descriptive criteria, but discussion led to a better agreement (kappa 0.60). We also found substantial, but not perfect, agreement between both experimental panels and the panel originally deciding on the diagnosis at the moment of inclusion in the DSEC. The experienced panel did slightly better than the panel whose members were not used to working in such a collaborative way. This was probably not because of the effect of memory, despite the fact that the experienced panel contained three of the four members of the original panel. All case descriptions had been anonymised and the time elapsed between inclusion in the DSEC and the experiment described here varied between one and six years. On the contrary, it is surprising that the agreement between the opinions of this panel at entry into the DSEC and some years later was not better than 0.72. Both the interrater and the "intra-panel" disagreement illustrated here suggest that the diagnosis of an isolated epileptic seizure may be extremely difficult and should always be looked at with some suspicion, especially in the context of a clinical research study.

For this study we had deliberately selected 100 cases with a 1:1 ratio between epileptic seizures on the one hand and unclear or non-epileptic events on the other. Although kappa statistics take into account the agreement due to chance, the results are influenced by the distribution of the possible diagnoses. In case of an askew distribution, kappa statistics will be lower than in case of a 1:1 ratio between the various diagnoses.[26] Therefore, the fair to moderate agreement rates found before discussion cannot be explained by an askew distribution between epileptic seizures versus unclear or non-epileptic events. One may even argue that our findings are biased towards a higher agreement.

Only in 24 cases was consensus reached on the syndrome diagnosis (table 5). A conspicuous discrepancy existed between the ways the panels used the ILAE classification. Panel B often tried to reach consensus on such classifications as "cryptogenic localisation-related epilepsy" or "idiopathic generalised epilepsy not otherwise defined". Panel A classified most of these seizures as "isolated seizure or isolated status". These classifications of both panels are safe when evidence concerning the nature of the seizure is lacking or inconclusive, but they do not contribute to our knowledge on the causal diagnosis of the child, the prognosis, or the way in which he or she should be treated. Only in the four children with benign childhood epilepsy with rolandic spikes did agreement exist on a syndrome with prognostic significance. King *et al* stated that syndrome diagnosis is possible in most patients presenting with only one seizure.[27] However, 45% of the patients in their study had suffered more than one seizure.[28] These patients were carefully excluded in our study by using standardised questionnaires.[6] Moreover, most patients in the study

of King *et al* were adults over 30 years old, so many had probably suffered a remote symptomatic partial seizure.[28–30] More recently, the CAROLE group also made a syndrome classification in patients with newly diagnosed epilepsy or only a single seizure.[2] In this study a panel made the diagnosis. However, the patients with a single seizure were much older than in our study (mean age 19 years) and most classifications were broadly defined as well. In our study, classification in a clinically relevant syndrome was possible only in a very small minority of children.

We know of only one study in which the reliability of the diagnosis of a first seizure was studied by assessing interrater agreement. This study was done in adults.[20] Other studies in epilepsy, in which kappa statistics were used, concerned generalised or partial seizure onset in adults,[31] and seizure classification[32] and syndrome classification in children,[33] all patients with multiple seizures. The study on seizure classification in children[32] showed poor interrater correlations, and suggested that specific criteria for the categorisation of symptoms could reduce the interrater variability. Combined with our results, this suggests that the best agreement could be obtained if the seizures were not only classified according to pre-defined criteria (like in our study), but also the symptoms categorised according to a standardised questionnaire to the patient and any witnesses of the seizure.

The study on interrater agreement on classification of childhood epilepsy syndromes[33] showed excellent agreement using the ILAE classification of epilepsy syndromes, although a substantial proportion of children were classified into relatively non-specific syndromes.[23] However, in this study only children with newly diagnosed epilepsy were classified, not children with a single seizure.

Even experienced paediatric neurologists frequently disagree about the diagnosis and classification of a first seizure in children. In this study the diagnosis was based on a careful written description made by experts with the aim of an extensive questionnaire. The agreement among neurologists may be even lower when they have to listen to the actual histories from the parents themselves.

Our results may at least partly explain the widely discrepant recurrence risks reported in first seizure studies.[10–19] In this study, the use of a panel was the best means to increase the interrater agreement. We recommend such an approach for research purposes, although even then in many cases the diagnosis will remain uncertain. However, better ways to diagnose first seizures are not currently available.

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Chapter 4

The accuracy of the diagnosis of paroxysmal events in children

Stroink H, van Donselaar CA, Geerts AT, Peters AC, Brouwer OF, Arts WF
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Abstract

Objective: To assess the accuracy of the diagnosis of epileptic seizures in children.

Methods: The Dutch Study of Epilepsy in Childhood is a prospective hospital-based study of 881 children referred because of possible seizures. The diagnosis was based on predefined descriptive criteria, as applied by a panel of three paediatric neurologists. Children with a definite other diagnosis were excluded. All children with unclear events were followed up for one year and children with seizures were followed up for two years to assess the accuracy of the diagnosis.

Results: In 170 of 224 children seen after a single event, the incident was classified initially as epileptic, in 54 as unclear. In none of the 170 children did the diagnosis prove to be wrong. In four of the 54 children, recurrent episodes enabled a definite diagnosis of epilepsy. In 412 of the 536 children seen with multiple events, an initial diagnosis of epilepsy was made. After follow-up, this initial diagnosis was probably incorrect in 19. In contrast, seven of 124 children with multiple unclear episodes at intake later received the diagnosis epilepsy.

Conclusions: A false positive diagnosis of epilepsy was made in 4.6%, whereas a definite diagnosis of epilepsy or seizure was delayed in 5.6% of children with multiple unclear events and in 7.4% of children with one unclear event.

Introduction

The diagnosis of a single seizure or epilepsy is based on a description of the episodes and may be subject to error. To prove that a single event was an epileptic seizure is often impossible. Generally accepted and validated diagnostic criteria are lacking. The widely used International Classifications of Seizures[1] and Epileptic Syndromes[2] provide no guidelines for the diagnosis of epileptic seizures. They only permit classification once the diagnosis has been made.[3 4] Surprisingly, most clinical or epidemiologic studies do not mention patients in whom the diagnosis proved to be incorrect.[5] The Dutch Study of Epilepsy in Childhood (DSEC) is a prospective hospital-based study of children with newly diagnosed possible single or multiple seizures.[6-8] A panel of three paediatric neurologists classified the events as epileptic seizures, unclear episodes, or events of definitely other origin. Children with one or more unclear events were followed up for one year and children with a diagnosis of a first seizure or epilepsy for five years. In this part of the study, we describe the accuracy of the initial diagnosis after one or more paroxysmal events.

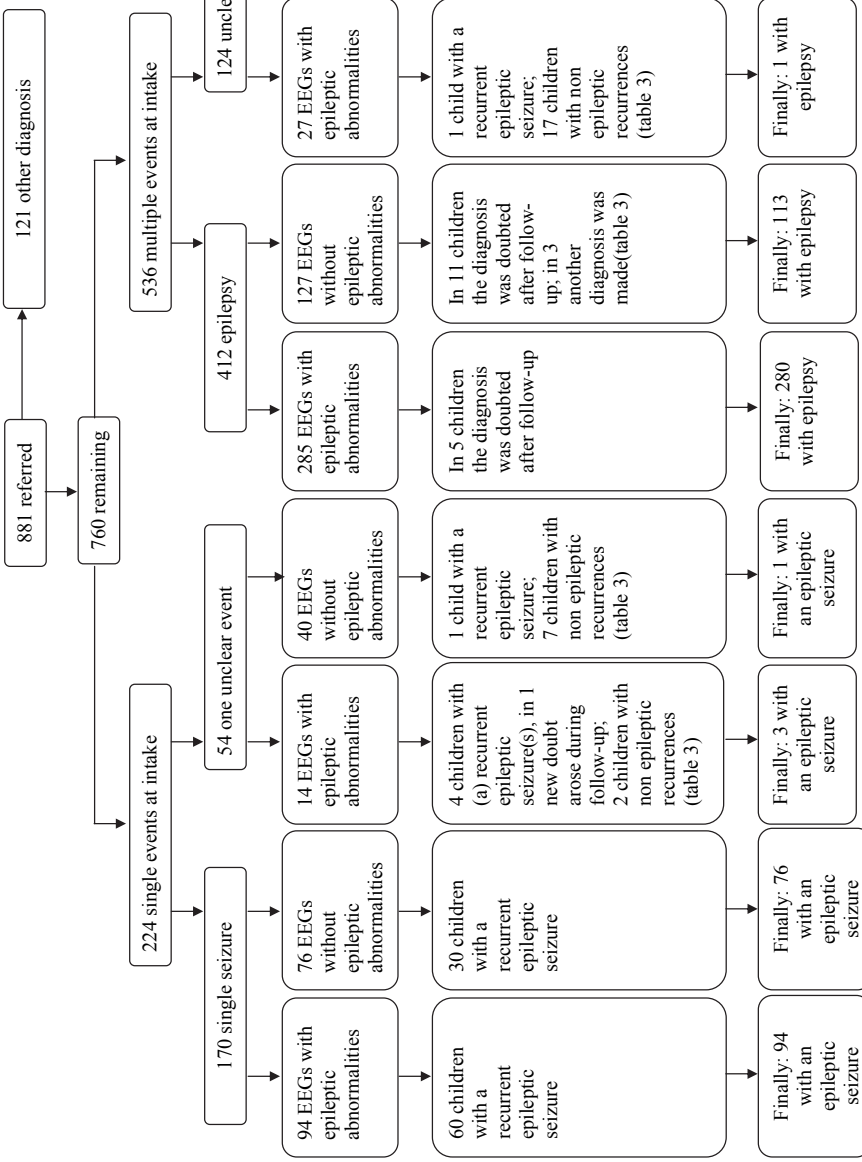

Figure. Flow chart of the 881 children with one or more possible seizures.

Patients and methods

The prospective multicenter hospital-based DSEC started in 1988. After informed consent, we enrolled consecutively all children aged one month to 16 years who were referred because of a possible single seizure or epilepsy. Most children were referred directly by their general practitioner or by the paediatricians of the participating hospitals (who routinely refer all children with possible seizures to the departments of paediatric neurology). Some were first seen in the emergency department. We excluded children with only neonatal, febrile, or other acute symptomatic seizures as well as children who were referred from other hospitals for a second opinion.

The attending paediatric neurologist completed an extensive questionnaire on the description of the events including postictal signs, possible provoking factors, medical history, and family history. In addition, the descriptions of the episodes according to the letters to the general practitioners were made available to the panel judging the diagnoses (see below). We performed a standard EEG in each child. If this did not show epileptiform discharges, a recording after partial sleep deprivation or, in small children, during a daytime nap was made. Details on the recording and classification of the EEG have been described elsewhere.[8] A brain CT scan was performed in all children unless anaesthesia was required or the child had idiopathic generalized epilepsy with absences. Seventy-two percent of the children with one seizure and 66% of the children with multiple seizures had a CT scan. In former publications on the DSEC, more extensive information concerning the results of imaging can be found.[6 7]

A panel of three of four paediatric neurologists with at least 10 years of experience in paediatric epilepsy (H.S., A.C.B.P., O.F.B., and W.F.M.A.) judged whether the description of the ictal events fulfilled the predefined descriptive diagnostic criteria for seizures as adapted from an earlier Dutch study in adults[9] (table E1 on the Neurology Web site). To prevent bias, none of the paediatric neurologists was allowed to judge his patients, but only those who were treated by one of the other panel members. These paediatric neurologists in 1988 founded the DSEC and have been involved in it since then. They discussed all 881 children referred during monthly sessions. Unanimous decisions were reached in all cases. The 121 children in whom another diagnosis was made were excluded. The study group consisted of 760 children: mean age 5.4 years, median age four years (25 to 75% range: two to nine years); 367 were boys. A flow chart of all children in the study and their subgroups is presented in the figure. For a single event, the diagnosis was based exclusively on the description of the event without knowledge of the results of the

EEGs or other ancillary studies. We considered a single unclear event in a child with an abnormal EEG not as an epileptic seizure, as epileptiform discharges are present in some children without any clinical seizures. In case of multiple events, however, the results of the EEGs were considered if the panel agreed based on their clinical experience that the events were suspect for seizures, although the criteria were not completely satisfied.

In the DSEC we followed up all children with a diagnosis of epilepsy for five years and all children with a single seizure for two years to assess the prognosis.[6 7] At two years, the accuracy of the original diagnosis was assessed. In an attempt to include all children with epilepsy in the DSEC, children with unclear events (including children with presumed pseudo-seizures) were followed for one year to assess whether new episodes might yield firm evidence for a definite diagnosis. An unclear event was defined as a paroxysmal event not considered as an epileptic seizure, but without another obvious explanation. After each new event, the patient was re-evaluated and the diagnosis reconsidered. Point estimates regarding false positive or false negative diagnoses are given with their 95% CIs. The CIs were calculated according to the efficient-score method (corrected for continuity).[10]

Results

Paroxysmal events

Of the 881 children in the study group, 121 received a definite other diagnosis and were excluded from follow-up (see the figure). A total of 224 children were referred because of a single event. In 170 of these 224, the panel diagnosed a single seizure (table 1); 90 of them had at least one more event. During the follow-up period, doubts on the diagnosis seizure arose in none of the children with recurrent events, whereas the diagnosis was maintained in all children without a recurrence (false positive rate, 0%; 95% CI, 0 to 2.8).

The panel was uncertain on the diagnosis of a first event in 54 children, of whom 14 had at least one more event. We eventually made a diagnosis of epilepsy after 1-year follow-up in five of these. After two years of follow-up, new doubts arose in one of these children. Her first event was associated with teeth brushing. We considered this event as uncertain diagnosis. Within 12 months, she had a second paroxysmal event. Her EEG showed epileptiform abnormalities; a diagnosis of epilepsy was made and an antiepileptic drug was prescribed. After about 20 months, a new event took place while her hair was being combed. Based on the description of this event and the circumstances during two of the three events (teeth brushing, hair combing) this was thought to be a hairdresser's syncope,[11] after which the

Table 1. Accuracy of the diagnosis of a single epileptic seizure.

		Diagnosis after follow-up	
		Epileptic seizure	Unclear/other diagnosis
	Diagnosis at entry		
First seizure	170	170	0
Unclear	54	4	50
Total	174	174	50
Positive predictive value	170/170	100%	(95% CI: 97.2; 100)
Negative predictive value	50/54	92.6%	(95% CI: 81.3; 97.6)
Sensitivity	170/174	97.7%	(95% CI: 93.8; 99.3)
Specificity	50/50	100%	(95% CI: 91.1; 100)

diagnosis of epilepsy was again rejected. Altogether, the false negative rate for the diagnosis of epilepsy was, therefore, four of 54 (7.4%; 95% CI, 2.4 to 18.7). The other nine children with a recurrence had syncope with myoclonic jerks (two) and benign paroxysmal vertigo, breath-holding spells, pseudo-seizures, and pavor nocturnus (one each), whereas in three children the diagnosis remained unclear. In the 40 patients without recurrence, the diagnosis remained unclear. Altogether, the sensitivity of the diagnosis "epileptic seizure" after a single paroxysmal event proved to be 97.7% and the specificity 100%.

At intake, the panel made a diagnosis of epilepsy in 412 children. This diagnosis was based on the description of the events in 367 children, and on the description combined with the EEG results in 45 children. During a 2-year follow-up period, doubts on the original diagnosis arose in 19 of 412 children (table 2; false positive rate for the diagnosis of epilepsy, 4.6%; 95% CI, 2.9 to 7.2). Three of them were initially included based on the description of the events combined with the results of the EEG, which means a false positive rate for the diagnosis of epilepsy in this group of 45 children of 6.7%; 95% CI, 2.3 to 17.9. The false positive rate for the diagnosis of epilepsy in the 367 children diagnosed exclusively based on the description was 4.4%; 95% CI, 2.7 to 7.0%. The final diagnoses for all children are given in table 3. The diagnosis at entry was unclear in 124 children seen with multiple events. Of these, 75 had at least one new episode during follow-up. After one year, a diagnosis of epilepsy was made in seven children (see table 2; false negative rate, 5.6%; 95% CI, 2.5 to 11.7), and in 36 another diagnosis was made. Table 3 presents the final diagnoses. In the group of 536 children with multiple events before intake, the sensitivity of the diagnosis "epilepsy" was 98.3%, the specificity 86.0%.

Table 2. Accuracy of the diagnosis of epilepsy.

		Diagnosis after follow-up	
		Epilepsie	Unclear/other diagnosis
	Diagnosis at entry		
Epilepsy	412	393	19
Unclear	124	7	117
Total	536	400	136
Positive predictive value	393/412	95,4%	(95% CI: 92.8; 97.1)
Negative predictive value	117/124	94.4%	(95% CI: 88.3; 97.5)
Sensitivity	393/400	98.3%	(95% CI: 96.3; 99.2)
Specificity	117/136	86.0%	(95% CI: 78.8; 91.2)

Based on the whole group of 760 children with single or multiple events, this means a sensitivity of (170+393)/(174+400) = 98.1% (95% CI, 96.5 to 99.0) and a specificity of (50+117)/(50+136) = 89.8% (95% CI, 84.3 to 93.6).

EEG results

The EEG might be used to increase the diagnostic accuracy of single paroxysmal events. Because the diagnosis of the single events rested entirely on its clinical description, it was possible to calculate the sensitivity and specificity of epileptiform EEG abnormalities in children with a single paroxysmal event after follow-up. In the group of 174 patients with an epileptic seizure or epilepsy as the final diagnosis (170 from the group with a single seizure and four from the group with one unclear event, excluding the patient in whom new doubt arose), 97 patients had an EEG with epileptic abnormalities (sensitivity 55.7%). In the group of patients with another diagnosis, or in whom doubt remained, 11 of 50 patients had an epileptiform EEG (specificity 78.0%;table 4). The presence of epileptiform EEG abnormalities was in accordance with the diagnosis of an epileptic seizure in 89.8% of the children.

The EEGs showed epileptiform abnormalities in 285 of the 412 children with multiple epileptic seizures. In 45 of those, the diagnosis of epilepsy was based on the combination of the description of the event and the EEG, because the events themselves were not sufficiently clear. However, after follow-up, the diagnosis was doubted in three of them. In addition, in the group of 240 children with an initial clinical diagnosis of epilepsy and epileptiform EEG abnormalities, two children

Table 3. Final diagnoses in 760 children referred with possible seizures.

	Initial diagnosis			
	First seizure, n=170	Uncertain first event, n=54	Epilepsy, n=412	Multiple uncertain events, n=124
Final diagnosis				
Epilepsy	90	4	393	7
Single seizure	80			
Unclear		43	6	81
Acute symptomatic seizures			1	1
Behavioral disturbances				6
Pseudo-seizures		1	2	12
Migraine				1
Benign paroxysmal vertigo		1		
Breath holding spell		1	1	2
Reflex anoxic seizure				2
Syncope with myoclonic jerks		2	2	8
Hair dresser's/teeth brushing syncope		1	1	
Daydreaming			3	3
Sleep apnea				1
Pavor nocturnus		1		
TIA (moya-moya)			1	
Reaction to fright			1	
Alternating hemiplegia			1	

appeared not to have epilepsy after follow-up. In 27 of 124 children with multiple uncertain events, either the first or the second EEG showed epileptiform abnormalities. Of these 27, definite epilepsy was eventually diagnosed in only one. Therefore, epileptiform abnormalities confirm the diagnosis of epilepsy after multiple events in 90.1%, and their absence refutes this diagnosis correctly in 46.9% (sensitivity, 70.3%; specificity, 77.2%; table 5).

Discussion

In this study rigid diagnostic standards were applied for the diagnosis of a single seizure or epilepsy in childhood. The diagnosis was based on consensus between the members of a panel of experienced paediatric neurologists, using predefined

Table 4. Diagnostic value of the EEG after a single paroxysmal event.

		Diagnosis after follow-up	
		Epileptic seizure	Other event
	EEG		
Epileptiform EEG	108	97	11*
No epileptiform EEG	116	77	39
Total	224	174	50
Positive predictive value	97/108	89.8%	(95% CI: 82.1; 94.5)
Negative predictive value	39/116	33.6%	(95% CI: 25.3; 43.1)
Sensitivity	97/174	55.7%	(95% CI: 48.0; 63.2)
Specificity	39/50	78.0%	(95% CI: 63.7; 88.0)

**including the patient in which new doubt arose during follow-up*

Table 5. Diagnostic value of the EEG after multiple events.

		Diagnosis after follow-up	
		Epilepsy	No epilepsy
	EEG		
Epileptiform EEG	312	281	31
No epileptiform EEG	224	119	105
Total	536	400	136
Positive predictive value	281/312	90.1%	(95% CI: 86.1; 93.0)
Negative predictive value	105/224	46.9%	(95% CI: 40.2; 53.6)
Sensitivity	281/400	70.3%	(95% CI: 65.5; 74.6)
Specificity	105/136	77.2%	(95% CI: 69.1; 83.8)

diagnostic criteria. Unfortunately, a gold standard to confirm or refute the diagnosis of a seizure or of epilepsy is lacking. Instead, we tried to disprove the original diagnosis by assessing whether new episodes during follow-up might lead to another diagnosis. Using this approach, we found a false positive rate for the initial diagnosis "single seizure" of 0% and for "epilepsy" of almost 5%. It should be noted that this method probably underestimates the number of incorrect diagnoses, because the diagnosis will not change if the child does not have a recurrence of the events during follow-up. Moreover, the low false positive rate may be explained

by the fact that the panel tended to prefer the diagnosis unclear and not seizure or epilepsy in case of any doubt or disagreement between the panel members.
In addition, we studied the fate of the children with an unclear diagnosis at enrollment. The false negative rate was 7.4% for children recruited after a single unclear event and 5.6% for children enrolled after more unclear events. In other words, irrespective of the fact that a child was enrolled after one or more unclear events, one of every 15 children was not recognized to have epileptic seizures. However, none of the children experienced any harm due to this delay.
Most of the children in whom the diagnosis seizures was changed during follow-up, as well as the children with unclear events in whom a diagnosis became obvious during follow-up, turned out to have a harmless paroxysmal disorder (see table 3). The majority was not harmed by unnecessary delay of medical treatment. The only exception was the child with TIAs based on moyamoya disease diagnosed initially as epilepsy.
In view of the rigid standards we used in the diagnostic process (diagnosis by a unanimous decision of a panel of three experienced paediatric neurologists with use of predefined criteria), the figures found in our study may be a minimum estimate for the errors in everyday clinical and research situations. This should be kept in mind when judging studies on the prognosis of single seizures and epilepsy in children. We recommend that in this type of research, the initial diagnosis should be reconsidered after sufficient follow-up. From a clinical point of view, however, a false negative diagnosis of epilepsy is probably less harmful for the patient than a false positive. A conservative approach in children with paroxysmal events of uncertain nature seems, as before, warranted.

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Chapter 5

Interobserver reliability of visual interpretation of electroencephalograms in children with newly diagnosed seizures

Stroink H, Schimsheimer RJ, de Weerd AW, Geerts AT, Arts WF, Peeters EA, Brouwer OF, Boudewijn Peters A, van Donselaar CA
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Abstract

The reliability of visual interpretation of electroencephalograms (EEG) is of great importance in assessing the value of this diagnostic tool. We prospectively obtained 50 standard EEGs and 61 EEGs after partial sleep deprivation from 93 children (56 males, 37 females) with a mean age of six years 10 months (SE 5 mo; range 4 mo-15 y 7 mo) with one or more newly diagnosed, unprovoked seizures. Two clinical neurophysiologists independently classified the background pattern and the presence of epileptiform discharges or focal non-epileptiform abnormalities of each EEG. The agreement was substantial for the interpretation of the EEG as normal or abnormal (kappa 0.66), almost perfect for the presence of epileptiform discharges (kappa 0.83), substantial for the occurrence of an abnormal background pattern (kappa 0.73), and moderate for the presence of focal non-epileptiform discharges (kappa 0.54). In conclusion, the reliability of the visual interpretation of EEGs in children is almost perfect as regards the presence of epileptiform abnormalities, and moderate to substantial for the presence of other abnormalities.

Introduction

The electroencephalogram (EEG) is an important tool in the diagnosis of children with epilepsy. EEG findings are used for the classification of epileptic syndromes and may determine the choice of anti-epileptic drugs. The presence of epileptiform discharges is a strong predictor for the risk of recurrence after a first seizure.[1-3]

The reliability (interobserver consistency or interobserver variation) and validity (accuracy) of a diagnostic or prognostic tool determine its value.[4] However, studies on the reliability of the visual interpretation of EEG findings are scarce.[5-10] Most investigations have focused on items not directly relevant to the treatment of patients with epilepsy. Observed agreement rates were often not corrected for agreement due to chance, making the results difficult to interpret. The visual interpretation of the EEG in adults with first seizures was subject to considerable interobserver variation.[11] Interobserver agreement on the correct site of seizure origin was excellent in patients with complex partial seizures.[10]

We investigated the reliability of the visual interpretation of the EEG in children with newly diagnosed unprovoked seizures. We tried to delineate those aspects that might serve to enhance or reduce interobserver variability.

Methods

This study is part of the prospective multicentre Dutch Study of Epilepsy in Childhood (DSEC). We enrolled all children aged one month to 16 years with one or more newly diagnosed unprovoked seizures who were referred to two university hospitals (Rotterdam, Leiden), a university children's hospital (Rotterdam), a general hospital (The Hague), and a children's hospital (The Hague) in The Netherlands. The DSEC was approved by the Ethics Committees of all involved hospitals, and informed consent was obtained in all cases before enrolment.[3 12]

A committee of three child neurologists judged whether the description of the ictal event(s) fulfilled predefined descriptive diagnostic criteria, and classified the seizures and epilepsies. We ordered a standard EEG and an EEG after partial sleep deprivation in each child on 16 to 21 channel machines with both referential and bipolar recordings using the International 10 to 20 electrode placement system. If the standard EEG showed epileptiform discharges, the recording after sleep deprivation could be cancelled. The standard EEG included intermittent photic stimulation and, if the child was able to cooperate, hyperventilation. The recording of the partial sleep deprivation EEG took place early in the afternoon after five hours of sleep the night before for children aged 11 to 15 years, and after seven hours of sleep for children aged three to 10 years. In younger children the second EEG was made at the time of their daytime nap.

EEGs were classified in accordance with a standardized questionnaire. The observers had no access to clinical data except the age of the child. The questionnaire contained items regarding the background pattern, the sleep stages, the occurrence of focal non-epileptiform abnormalities, and the presence of epileptiform discharges. The following questions had to be answered: is the EEG normal? If not, is the background pattern normal? Are epileptiform discharges present? Are focal non-epileptiform abnormalities present?

If epileptiform discharges were present, the clinical neurophysiologist had to decide whether these discharges consisted of spikes or spike-waves, whether the frequency of the discharges was more or less than 3Hz, whether the discharges occurred more or less often than once per 20 seconds, and whether the discharges were generalized or (multi)focal. Paroxysmal fast activity or electrodecremental activity did not occur in this material but would have been scored as epileptiform. Intermittent rhythmic delta activity was not scored as epileptiform but as focal non-epileptiform abnormality, and frontal intermittent rhythmic delta activity as part of a ground pattern abnormality.

The EEGs were classified initially by the clinical neurophysiologist from the hospi-

tal in which the recording was done. We mailed the EEGs for a second judgement at random to one of five clinical neurophysiologists from the other participating hospitals. The second observer scored the EEG without access to the initial classification. They used a fixed protocol to classify the EEGs. All five observers were experienced full-time working clinical neurophysiologists.

The EEGs were obtained from 93 children (56 males, 37 females) with one or more seizures out of the cohort of the DSEC (mean age 6y 10mo; range 4mo-15y 7mo; (SE 5mo); 7.5% were aged less than Iy, 33.4% l-6y, 49.4% 6-12y. and 9.7% 12-l6y). We started with a sample of 72 EEGs; 16 were randomly chosen from the EEGs scored as normal and 56 from the EEGs scored as not normal by the first observer. The participating clinical neurophysiologists were not aware of the distribution of the number of normal or abnormal EEGs, nor in which order they were submitted for their judgement.

The distinction between focal non-epileptiform abnormalities and abnormal background patterns often led to disagreement. After discussion with the participating neurophysiologists we defined non-epileptiform abnormalities as focal if they were restricted to a maximum of three adjacent electrodes. We then took a second random sample of 39 EEGs (37 abnormal and two normal recordings according to the first observer).

We used kappa statistics to adjust the observed interobserver agreement ($p_{observed}$) for the proportion of agreement due to chance (P_{chance}): $kappa=(p_{observed}-p_{chance})/(1-p_{chance})$.

The value of kappa ranges from +1, denoting perfect agreement, to -1 for total disagreement. A value of 0 indicates that the agreement is not better than would be expected by chance alone (Cohen 1960, Schouten 1982).[13] [14] Kappa values of 0 to 0.2 are considered to be slight, 0.2 to 0.4 fair, 0.4 to 0.6 moderate, 0.6 to 0.8 substantial, and 0.8 to 1.0 almost perfect.[4] Because the EEGs were scored by two out of a group of five observers we used group-kappa statistics.

Results

Table 1 illustrates how often the observers agreed on each conclusion in the first sample of 72 EEGs. The kappa statistics for agreement on whether the EEG was abnormal or normal was 0.66, for the presence of epileptiform abnormalities 0.83, for the abnormality of the background pattern 0.53, and for the presence of focal non-epileptiform abnormalities 0.38.

Disagreement on epileptiform abnormalities existed when there were only a few discharges and these discharges were illdefined, for example in the case of slow

waves intermingled with sharp waves, or slow waves with 'notches' on the descending or ascending slope. Epileptiform discharges sometimes occurred during drowsiness and could not be well differentiated from small non-specific spikes. Some occurred only at the start of photic stimulation without a clear photoconvulsive response.

Disagreement on the background pattern was caused by two basic well-known problems. The first is the question of whether the background pattern is too slow for age. Because of the 'grey zone' between normal and abnormal patterns in children, this problem contributed to more than 90% of the disagreement on this item. The second problem is the interpretation of posterior slow rhythms, especially when they occur asymmetrically. Some observers classified these as normal variants, others as focal abnormalities.

Focal slowing on one side without phase opposition was another problem. Some classified this as a focal abnormality, others as an asymmetry of the background pattern. Focal slowing that was independent of spike and spike-wave discharges but with the same localization was scored separately as a focal non-epileptiform abnormality by some, whereas others scored this only as an epileptiform abnor-

Table 1. Interobserver agreement and kappa statistics in classification of each end-conclusion on first sample of 72 electroencephalograms (EEGs).

	Observer 2							
	Normal		*Epileptiform discharges*		*Abnormal background pattern*		*Focal non-epileptiform Abnormalities*	
	Yes	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
Observer 1								
Yes	13	3	35	3	16	12	10	9
No	6	50	3	31	3	41	8	45
p observed	0.88		0.92		0.79		0.76	
p chance	0.63		0.50		0.55		0.62	
Kappa	0.66		0.83		0.53		0.38	
SE kappa	0.11		0.07		0.11		0.13	

Thirty standard EEGs and 42 EEGs after partial sleep deprivation were recorded. Observer 1 and Observer 2 are the first two of a group of five observers. SE, standard error.

Table 2. Interobserver agreement and kappa statistics in classification of each end-conclusion in the second sample of 39 electroencephalograms (EEGs)[a].

	Observer 2							
	Normal		*Epileptiform discharges*		*Abnormal background pattern*		*Focal non-epileptiform Abnormalities*	
	Yes	*No*	*Yes*	*No*	*Yes*	*No*	*Yes*	*No*
Observer 1								
Yes	1	1	20	4	22	2	14	4
No	1	36	2	13	2	13	2	19
p observed	NA		0.82		0.87		0.77	
p chance	NA		0.51		0.53		0.50	
Kappa	NA		0.63		0.73		0.54	
SE kappa	NA		0.13		0.12		0.14	

[a]After redefining the distinction of abnormal background patterns from focal non-epileptiform abnormalities. Observer 1 and Observer 2 are the first two of a group of five observers. Twenty standard EEGs and 19 EEGs after partial sleep deprivation were recorded. NA, not applicable. SE, standard error.

mality. Disagreement about focal abnormalities proved to be more a problem of definition than of interpretation.

Interobserver consistency on the occurrence of abnormal background patterns proved to be moderate and agreement on focal non-epileptiform abnormalities proved to be fair. After discussion with the participating neurophysiologists we defined abnormalities as focal if they were restricted to a maximum of three adjacent electrodes. We then took a second sample of 39 'new' EEGs: 37 at random from the EEGs scored as abnormal by the first observer, and two at random from the EEGs scored as normal. Table 2 shows the agreement of the observers on each conclusion. The agreement rates for the occurrence of an abnormal background pattern improved from 0.53 to 0.73, and for the occurrence of focal non-epileptiform abnormalities from 0.38 to 0.54. Agreement rate on the presence of epileptiform abnormalities was 0.63 for this sample, and 0.76 for all 111 EEGs. Of all EEGs on which the observers agreed about the presence of epileptiform abnormalities, 74% showed focal or multifocal epileptiform activity and 12% generalized epileptiform activity; 14% showed focal as well as generalized discharges. Because the new

sample contained only two normal EEGs, it is not useful to assess interobserver agreement on the question of whether the EEG was normal or abnormal.
Agreement rates for the interpretation of the standard EEG proved to be better than those for the partial sleep deprivation EEG for all categories.

Discussion

Absolute criteria for the clinical significance of a given kappa value are lacking and the prevalence of a positive test result may influence the kappa.[4 15] The values found in our study may be interpreted as substantial for the interpretation of the EEG as normal or abnormal, and almost perfect for the presence of epileptiform abnormalities. Agreement was substantial for the occurrence of abnormal background patterns, and moderate for focal non-epileptiform abnormalities after adjustment of the definition used to delineate these two aspects.
These agreement rates for epileptiform abnormalities and background pattern are clearly above the usual level for clinical agreement. For most clinicians the presence of epileptiform discharges will be the most important question. For focal non-epileptiform abnormalities, after adjustment of the definition, kappa reaches a usual level for clinical agreement[4]. Moreover, nowadays magnetic resonance imaging is the investigation of choice if focal structural lesions are suspected.
The examiner and the examined[4] may cause interobserver variation. Different examiners may have different opinions on the interpretation of certain graphical elements and some phenomena may be difficult to interpret. We confined ourselves to 'coarse' conclusions because these might be used to guide the clinical management of the children.
Differences in interpretation could not be resolved into one item on which opinions differed repeatedly. Interpretation of EEGs after partial sleep deprivation proved to be more difficult as a result of ambiguity of sleep or drowsiness phenomena. Other differences in opinion were caused by well-known problems such as the question of whether the background pattern is normal for age. The definition of focal non-epileptiform abnormalities proved to be particularly difficult. In a previous comparable study in adults with first epileptic seizures, agreement rates were moderate.[11] This might be explained by differences in the population studied and hence by the nature of the EEG abnormalities. If epileptiform discharges occur, they are more frequent in children than in adults.
The classification of the background pattern in children is more difficult because of the question of whether the background pattern is too slow for age. Comparison with other studies on the reliability of visual interpretation of EEGs is difficult

because different categories were used, the populations concerned were not comparable to ours, or the observed agreement rates were not corrected for agreement due to chance.[6-10]

Conclusion

The reliability of the visual interpretation of the EEG in accordance with the criteria used in our study in children with newly diagnosed unprovoked seizure(s) is almost perfect for the presence of epileptiform discharges, substantial for abnormal background patterns, and moderate for focal non-epileptiform abnormalities. The agreement rates for non-epileptiform abnormalities can be improved by the use of well-defined descriptive criteria.

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Part II
Prognosis

Chapter 6

The first unprovoked, untreated seizure in childhood: A hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence

Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters AC, van Donselaar CA
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Abstract

Objective: To assess the accuracy of the diagnosis of a first unprovoked seizure in childhood, the recurrence rate within two years, the risk factors for recurrence, and the long term outcome two years after recurrence.

Methods: One hundred and fifty six children aged one month to 16 years after a first seizure, and 51 children with a single disputable event were followed up. The diagnosis of a seizure was confirmed by a panel of three child neurologists on the basis of predescribed diagnostic criteria. None of the children was treated after the first episode.

Results: Five children with a disputable event developed epileptic seizures during follow up. The diagnosis did not have to be revised in any of the 156 children with a first seizure. The overall recurrence rate after two years was 54%. Significant risk factors were an epileptiform EEG (recurrence rate 71%) and remote symptomatic aetiology and/or mental retardation (recurrence rate 74%). For the 85 children with one or more recurrences, terminal remission irrespective of treatment two years after the first recurrence was >12 months in 50 (59%), <six months in 22 (26%), and six to 12 months in 11 (13%) and unknown in two (2%). Taking the no recurrence and recurrence groups together, a terminal remission of at least 12 months was present in 121 out of the 156 children (78%).

Conclusions: The diagnosis of a first seizure can be made accurately with the help of strict diagnostic criteria. The use of these criteria may have contributed to the rather high risk of recurrence in this series. However, the overall prognosis for a child presenting with a single seizure is excellent, even if treatment with antiepileptic drugs is not immediately instituted.

Introduction

Despite several studies,[1-12] there is still no definite answer concerning the management strategy of children with a first unprovoked epileptic seizure. Besides knowledge of the risk of recurrence and the predictive factors, knowledge of the long term prognosis after a recurrence is a prerequisite for the formulation of adequate treatment guidelines.

Reported estimates of the recurrence risk after a first unprovoked seizure in childhood range from 23% to 71% after three years.[2 4] The main factors associated with a higher risk of recurrence are an EEG showing epileptiform abnormalities and remote symptomatic aetiology.[12]

Possible causes for the widely diverging recurrence rates are differences of study

design, case definitions used for ascertainment, referral patterns within the population studied, delay after the seizure before inclusion in the study, and the prevalence of various potential risk factors within the population studied.[12 13] A surprising factor is the absence of discussion about diagnostic uncertainty. In none of the studies mentioned above have diagnostic criteria been used to differentiate between epileptic and non-epileptic first fits. In particular in young children and infants the differential diagnosis of a seizure is extensive, and confirming or refuting the epileptic origin of such an event may be quite difficult.

It is still a matter of discussion whether or not children should be treated after a first unprovoked seizure. Treatment after a first fit may lead to a significant decrease in the risk of relapse.[11] Whether early suppression of seizures contributes to a better long term outcome after recurrence, however, has not yet been defined.

This study was designed to assess prospectively the risk of recurrence in an accurately diagnosed cohort of children with an untreated first unprovoked seizure, to identify predictive factors for such a recurrence, and to estimate the long term outcome of those children who had a relapse. To improve diagnostic accuracy, we used predefined diagnostic criteria formulated in simple descriptive terms, as well as the expert opinion of a panel of paediatric neurologists.

Methods

Patients

Most patients in this prospective study were derived from a consecutive series of 881 children, aged between one month and 16 years, who were referred with one or more possible unprovoked seizures, or at least one episode of status epilepticus, to one of the four participating hospitals: two university hospitals, one children's hospital, and one general hospital in the southwest region of The Netherlands. This cohort forms the basis of the Dutch Study of Epilepsy in Childhood (DSEC), which tries to answer several clinical-epidemiological questions about newly diagnosed childhood epilepsy.[14] Inclusion for the first seizure part of the DSEC started 1 January 1988 and ended 1 August 1992. Children were mainly referred by general practitioners, by paediatricians of the participating hospitals, or were first seen in the emergency room of the participating hospitals. All children with possible seizures were recruited, but to be eligible for entry into the study, a committee of paediatric neurologists (HS, WFA, OFB, and ACBP, excluding the attending neurologist) had to agree that the description of the single episode, as described by the child, or an eye witness, or both concurred with predefined descriptive diagnostic criteria of an epileptic seizure, adapted from Van Donselaar *et al*,[15] without having

any knowledge of the results of the EEG. The committee excluded children with a clear non-epileptic event such as a reflex anoxic seizure or syncope. Children with an event classified by the committee as "disputable" were followed up separately for one year to test our diagnostic procedure.

Children with a seizure due to an acute neurological insult (meningitis, trauma), metabolic disturbances, or fever (temperature over 38.0^{0}C) were excluded. Children with a history of earlier seizures other than neonatal or febrile seizures; with a single episode of status epilepticus; with a recurrence within 24 hours; or with an interval between the seizure and the first visit to the hospital of more than three months, were not included in the first seizure part of the DSEC, but in the study part on the general prognosis of newly diagnosed epilepsy in childhood (published later on).[16 17] Of the remaining 170, we excluded 10 children because of possible fever reported by the parents (precise temperature not known). Four other children were excluded because they had been treated with antiepileptic drugs. One child was treated mistakenly after only one seizure; three other children were treated because of multiple recurrences associated with fever, but they had not had unprovoked recurrences at that time. Finally 156 children remained for inclusion.

Classification

The committee classified seizures according to the revised classification of the International League Against Epilepsy (ILAE).[18] The aetiology was classified as remote symptomatic if the child was known to have a static encephalopathy caused by a prenatal or perinatal encephalopathy or a prior neurological insult such as infection, stroke, or cerebral trauma. Children with mental retardation (estimated IQ below 70) were included in this group. According to the recent guidelines on epidemiological research of the ILAE,[19] patients with a genetically determined type of epilepsy manifesting through a single seizure were called idiopathic. All other children were considered cryptogenic. In this analysis idiopathic and cryptogenic cases were grouped together. This seems to be justifiable, because it is usually not possible to distinguish between them after only one seizure.[20]

Additional investigations

A standard EEG (EEG1) was obtained in all patients. If it did not disclose epileptiform abnormalities, a second EEG (EEG2) was performed after partial sleep deprivation, or during the daytime sleep in very young children. All EEGs were classified as normal or abnormal and scored for the presence of epileptiform abnormalities (focal and generalised spikes or spike and wave complexes), and other abnormalities (abnormal background pattern or focal non-epileptiform abnorma-

lities) by clinical neurophysiologists who were unaware of the clinical data. Brain CT was scheduled in all children if possible without anaesthesia. The decision to perform CT in the remaining children was up to the child neurologist.

Follow up

We followed up all children with a single seizure on a regular basis for 24 months by hospital visits and by telephone interviews. After a recurrence, defined as any unprovoked seizure after inclusion into the study, the children were seen again and a detailed history was taken. We followed up all these children after their recurrence for 24-72 months (mean 42, median 44, 25, and 75 percentile: 30; 54 months) until 1 August 1994, with the exception of two children who were lost 0 and 10 months after the recurrence.

No antiepileptic drugs were prescribed after the first seizure. The decision whether or not to start treatment after one or more recurrences was left to the attending paediatric neurologist.

The outcome was measured by two methods. Firstly, the duration of the seizure free period irrespective of treatment existing at two years after the first recurrence (terminal remission, TR) according to the following definition: excellent, no recurrence at all; good, TR at least 12 months; moderate, TR six to 12 months; poor, TR less than six months. Secondly, the maximum period of seizure freedom after recurrence irrespective of treatment (longest remission ever, LRE) according to a slight modification of the definition of Arts *et al*:[21]excellent, no seizures at all; good, LRE at least 12 months; moderate, LRE six to 12 months; poor, LRE less than six months.

Fifty one children with a single ictal event in whom no clear diagnosis could be made were followed up for one year to assess the accuracy of our diagnostic procedure.

Analysis

Kaplan-Meier survival analysis was used for calculation of the recurrence rates.[22] Univariate and multivariate analyses were performed using Cox's proportional hazards model.[23] The multivariate analysis was done with a full model and with stepwise backward elimination of variables. In the second, we used simple parameter coding, and a probability of removal of 0.10.

Informed consent

The study was approved by the ethics committees of all involved hospitals, and informed consent was obtained in all cases before enrolment.

Table 1. Association between a priori defined risk factors and risk of recurrence after a first seizure: univariate analysis using Cox proportional hazards regression model.

Risk Factors	Rate ratio	95% CI	P Value
Age at intake (n=156)	1.02	0.97-1.08	0.43
Patient delay (n=156)	0.99	0.97-1.00	0.06
Sex:			
Male (n=70)	1.00#		
Female (n=86)	0.73	0.48-1.12	0.15
Seizure type (description only):			0.95
Tonic clonic (n=142)	1.00#		
Complex partial (n=8)	0.99	0.36-2.72	0.99
Simple partial (n=6)	1.18	0.43-3.23	0.75
Seizure type (description and EEG combined):			0.19
Generalised (n=84)	1.00#		
Partial (n=63)	1.50	0.97-2.33	0.07
Undefined (n=9)	1.35	0.53-3.41	0.53
Aetiology:			
Idiopathic/cryptogenic (n=129)	1.00#		
Remote symptomatic (n=27)	2.25	1.37-3.70	0.001*
EEG1:			0.0003*
Normal (n=57)	1.00#		
Epileptiform (n=68)	2.45	1.49-4.03	0.0004*
Other abnormalities (n=31)	1.02	0.52-2.02	0.94
EEG2:			0.05*
Normal (n=39)	1.00#		
Epileptiform (n=20)	1.05	0.44-2.51	0.91
Other abnormalities (n=13)	2.70	1.16-6.28	0.02*
EEG1 and EEG2 combined:			0.02*
Normal (n=43)	1.00#		
Epileptiform (n=88)	2.04	1.18-3.52	0.01*
Other abnormalities (n=25)	1.18	0.55-2.53	0.66
CT-brain:			0.03*
Normal (n=100)	1.00#		
Abnormal (n=12)	1.96	1.00-3.87	0.05*
Not done (n=44)	0.69	0.41-1.17	0.17
Family history for epilepsy:			
Negative (n=141)	1.00#		
Positive (n=15)	0.77	0.35-1.66	0.50
History of febrile seizures:			
Negative (n=139)	1.00#		
Positive (n=17)	0.82	0.40-1.70	0.59
State of arousal:			0.34
Awake (n=100)	1.00#		
Sleep (=42)	0.73	0.44-1.22	0.23
On awakening (n=9)	1.04	0.42-2.59	0.94
Unknown (n=5)	1.87	0.67-5.17	0.23

** Statistically significant # Reference category*

Results

Seventy of the 156 included children were boys (table 1); the mean age at intake was 7.1 years (median 6.9; range 0.2-15.6 years) (figure 1); 49% of the children were seen within 24 hours after the seizure; 71% within one week; 89% within one month; and all were seen within 81 days.

According to the predefined descriptive criteria, 142 children had a generalised tonic-clonic seizure with or without partial onset, eight a complex partial seizure, and six a simple partial seizure without secondary generalisation. The standard EEG showed abnormalities in 99 (63%).

Diagnostic accuracy

We excluded 51 children with a single episode, judged by the committee as being of disputable origin (table 2). One child was lost to follow up. Five children (10%) proved to have epilepsy during a one year follow up. Three of these had epileptiform discharges in their standard EEG. Four children with a disputable event had been found unconscious in a possible postictal state, without a seizure itself having been witnessed. Three other children had had a seizure according to the committee, but the description did not meet the a priori descriptive criteria. These

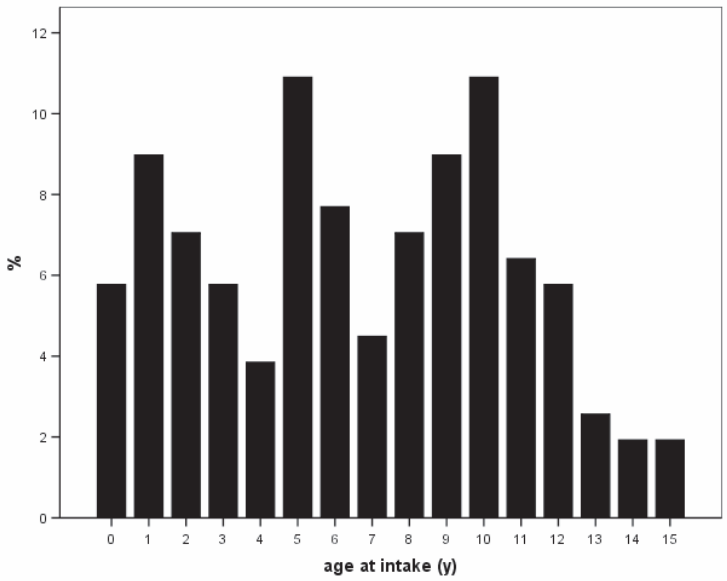

Figure 1. Distribution of ages of 156 children at the time of their first unprovoked seizure.

seven children did not have a recurrence within one year, although two had epileptiform discharges on EEG1. The other children turned out to have vasovagal syncopes (13), blue or pale breath holding spells (two), benign paroxysmal vertigo (one), pseudoseizures (one), pavor nocturnus (one), or the nature of the episodes remained unresolved during follow up (20). Yet, three of them had epileptic discharges on the EEG. This was interpreted as a coincidence.
The diagnostic accuracy in the 156 children in whom the panel confirmed the diagnosis of a seizure was high. The diagnosis was not revised In any of the children with a recurrence of the event.

Risk of recurrence

The overall recurrence rate was 40% (95% confidence interval (95% CI) 33-48%) at six months; 46% (95% CI 38-53%) at one year; and 54% (95% CI 46-62%) at two years (fig 2). Significant predictive factors for recurrence were results of EEG1 and EEG2, aetiology, and CT (table 1).
Children with epileptiform discharges in their EEG1 (n=68; 44%) had a recurrence rate of 71% at two years (95% CI 60-81%); in children with a normal EEG1 (57) this was 40% (95% CI 28-53%), and in those (31) with an otherwise abnormal EEG1 42% (95% CI 25-59%) (fig 3). A second EEG, performed in 72 of 88 children who had no epileptiform discharges on EEG1, showed epileptiform abnormalities

Table 2. Outcome of 51 children with a disputable episode.

Probable diagnosis after 1 year	*n*	*Epileptiform discharges on EEG1*	*Children with recurrences*
Epilepsy	5	3	5
Found in supposedly postictal state	4	1	0
Seizure not meeting the criteria	3	1	0
Syncope	13	1	2
Breath holding spells	2	0	1
Benign paroxysmal vertigo	1	0	1
Pseudoseizures	1	0	1
Pavor nocturnus	1	0	1
No diagnosis	20	2	2
Lost	1	0	?
Total	51	8	13

in another 20 children (28%). Aetiology also proved to be a significant predictive factor for recurrence (fig 4). Recurrence rate at two years was 50% (95% CI 41-59%) in 129 children with a cryptogenic or idiopathic seizure, and 74% (95% CI 57-91%) in 27 children with remote symptomatic aetiology or mental retardation without known cause (table 1).

Brain CT was obtained in 112 children. The abnormalities (mostly atrophy) found in 12 children were without therapeutic consequences. Recurrence rate at two years was 75% (95% CI 51-100%) in those with abnormal CT findings, 56% (95% CI 46-66%) in the children with normal CT and 43% (95% CI: 29-58%) in the children in whom no CT was performed.

No significant influence on the recurrence rate was found for the other variables investigated (table 1).

Full model multivariate analysis was carried out with 11 variables. An epileptiform EEG1 was the most important predictive factor for seizure recurrence. Remote symptomatic aetiology was also significantly associated with risk of recurrence. After stepwise backward elimination of variables not contributing to the model, aetiology, EEG1, and the sleep state remained. EEG1 was the most significant variable.

Long term outcome after recurrence

At the end of the follow up of all children, 71 children (46%) had an excellent outcome without any recurrent seizure. Sixty nine of the 85 children with a recurrence were treated with antiepileptic drugs. Of the children with a recurrence, 27 (32%) had an excellent outcome, 23 (27%) a good, 11 (13%) a moderate, and 22 (26%) a poor outcome defined by terminal remission. Two children were lost 0 and 10 months after recurrence. This means that of all admitted children with a single seizure 121 (78%) had an excellent or good outcome. According to the definition of Arts *et al*[19] (LRE), the outcome was excellent in 27 children (32%) with a recurrence, good in 32 (38%) moderate in 17 (20%) and poor in only seven (8%). The outcome was excellent or good in 130 (83%) of all admitted children.

Discussion

When the clinician is confronted with the problem of a child who has experienced a single episode that seems to be of epileptic origin, some questions have to be considered. Was the event really epileptic? If so, what is the risk of more seizures occurring? Should anticonvulsant treatment be offered and with what goal? What is the long term outcome with or without treatment?

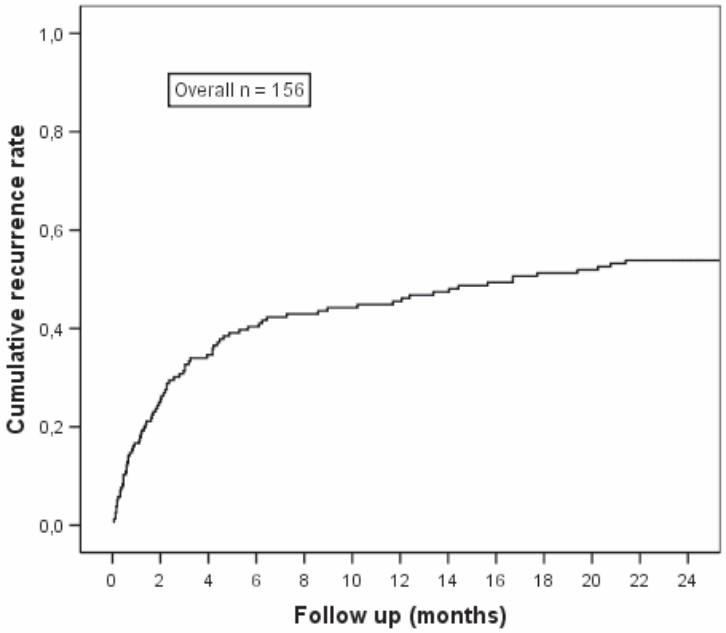

Figure 2. Probability of recurrence of seizure after a first unprovoked seizure.

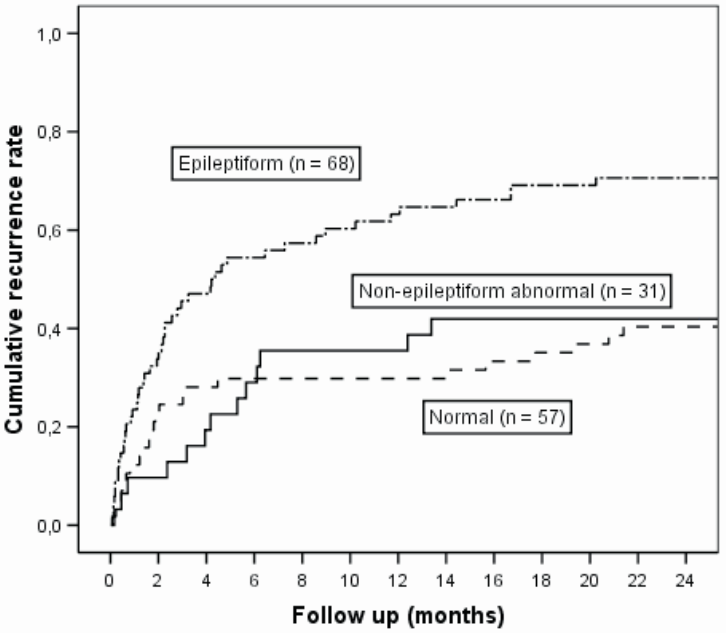

Figure 3. Probability of recurrence of seizure after a first unprovoked seizure as function of the standard EEG.

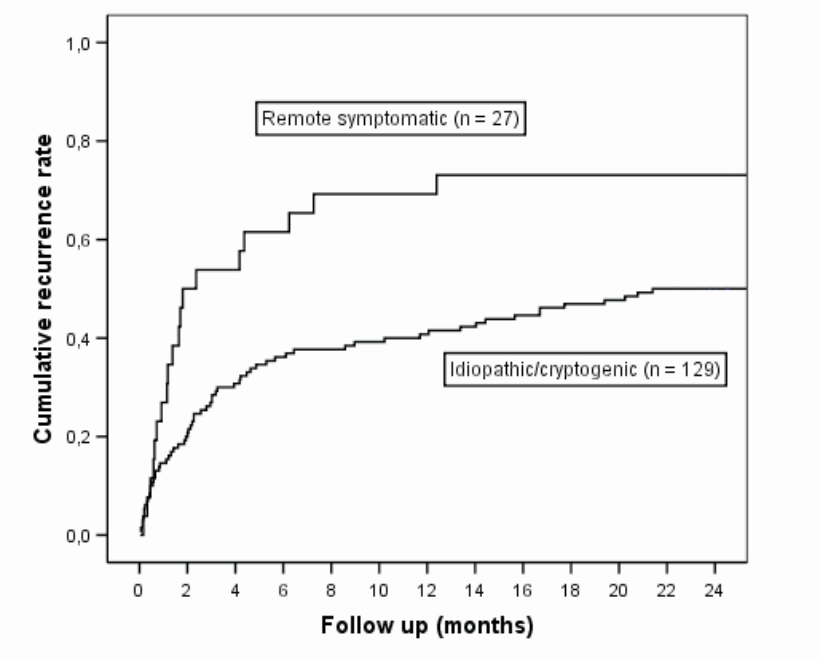

Figure 4. Probability of recurrence of seizure after a first unprovoked idiopathic or cryptogenic seizure and after a first unprovoked remote symptomatic seizure.

As the diagnosis of a first epileptic seizure may have a great impact on the child and its parents, a correct diagnosis is of the utmost importance. Criteria for the diagnosis single seizure are not discussed in earlier studies in children. We used simple descriptive diagnostic criteria as well as discussion in a committee of three paediatric neurologists to determine whether the ictal event was epileptic or not. This method has been shown to increase the reliability of the diagnosis by reducing the between rater variability.[15] The origin of the ictal event was considered to be unclear in 51 children. During a one year follow up, only five (10%) of them developed epilepsy versus 72 (46%) of the children included with a first seizure. If we had diagnosed those five children correctly on admission and had not included children with a false positive diagnosis the recurrence rate at one year would in the worst case alter only slightly to 77 of 161 (48%). Because the much greater disadvantages of a false positive diagnosis a low number of false negative diagnoses is in our opinion preferable to inclusion of falsely positive diagnosed children. In the patients with a questionable description of the event, the EEG did not always contribute to the correct diagnosis, as only three out of eight disputable patients with an epileptiform EEG1 developed epilepsy within one year.

The overall recurrence rate of 54% at two years after a first unprovoked seizure found in this study is higher than in other recent prospective studies[3 8 9] and in a recent meta-analysis.[12] Factors that may have increased the recurrence rate in our study are the withholding of antiepileptic drug treatment after the first fit, and the high diagnostic accuracy by the use of strict diagnostic criteria. Furthermore, 49% of the children were seen within 24 hours and 71% within one week. Therefore, the number of children who were not included because of an early recurrence, was probably small.

The risk factors for recurrence identified in this study were similar to those reported by others.[12] An EEG with epileptiform abnormalities proved to be the main risk factor for recurrence. Other factors associated with a higher risk of recurrence found in this study were remote symptomatic aetiology, or mental retardation, or both and abnormal CT. The children in whom no CT was carried out, had the lowest recurrence rate. Obviously, the neurologists selected children for CT on clinical grounds. In our opinion CT is not routinely indicated for children presenting with a first seizure.

Remarkably, whereas others have found that the occurrence of a first seizure during sleep is associated with an increased risk of recurrence,[24] we found the opposite. We think that the use of strict criteria and discussion of each child by the expert committee lowered the number of children with non-epileptic events. Non-epileptic events are less likely to occur during sleep. This may have caused a bias in other studies.

Despite the relatively high recurrence rate, most children did well in the end. Our strategy to delay treatment after the first unprovoked seizure in our study group of 156 children led to a rather high recurrence rate of 54%. The long term outcome was poor in only 22 out of 156 children (14%) using terminal remission as the criterion. Many of the children with a poor outcome had infrequent generalised tonic-clonic or rolandic seizures, of which one or two coincidentally occurred during the final half year of the two year follow up. This explains the better outcome in terms of longest remission ever.[21]

There is controversy over whether treatment should be offered after a single seizure. In Europe, children with single unprovoked epileptic seizures are usually not treated. The current clinical practice is to defer treatment until two or more seizures have occurred, although children perceived to be at high risk for recurrence may be treated after a single fit. The Italian First Seizure Trial Group carried out a controlled randomised trial of anticonvulsant therapy after a first generalised tonic-clonic seizure that occurred within the preceding seven days, in a large cohort including 113 children.[11] After two years, the recurrence rate for these children

was significantly lower in the treated group (25% *v* 51%). Treatment after the first seizure did not, however, improve long term prognosis.[25]

For an answer to the question whether treatment should be started in a child presenting with a first epileptic seizure, more knowledge of the long term outcome after recurrence is urgently needed. From our study, it may be concluded that the indication for starting long term treatment with AEDs after a single seizure in childhood is weak, because the risk of developing intractable epilepsy is already low. Immediate treatment will probably not further improve long term prognosis.[25] Treatment of all children after a single seizure therefore means treatment of many who will never have a second seizure; treatment of many whose epilepsy will have a benign course irrespective of treatment; and treatment of only a small minority in the hope of preventing them becoming intractable. Unfortunately, we are not able to predict which children will do badly after a single seizure. This would allow us to restrict treatment to these children. At this time, it seems to be advisable to delay long term anticonvulsant treatment until recurrent seizures are adversely affecting the child's life without signs of spontaneous remission. In so doing many children will never have to start long term treatment.

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Chapter 7

Status epilepticus in children with epilepsy

Stroink H, Geerts AT, van Donselaar CA, Peters ACB, Brouwer OF, Peeters EA, Arts WF Epilepsia 2007;48:1708-1715.

Abstract

Purpose: To study course and outcome of epilepsy in children having had a status epilepticus (SE) as the presenting sign or after the diagnosis.
Methods: A total of 494 children with newly diagnosed epilepsy, aged one month through 15 years, were followed prospectively for five years.
Results: A total of 47 Children had SE. Forty-one of them had SE when epilepsy was diagnosed. For 32 (78%), SE was the first seizure. SE recurred in 13 out of 41 (32%). Terminal remission at five years (TR5) was not significantly worse for these 41 children: 31.7% had a TR5 <1 year versus 21.2% of 447 children without SE. They were not more often intractable. Five out of six children with first SE after diagnosis had a TR5 <1 year. Mortality was not significantly increased for children with SE. Independent factors associated with SE at presentation were remote symptomatic and cryptogenic aetiology, and a history of febrile seizures. Children with first SE after inclusion more often had symptomatic aetiology.
Conclusions: Although we find a trend for shorter TR5 in children with SE at presentation, outcome and mortality are not significantly worse. Aetiology is an important factor for prognosis. Children with SE during the course of their epilepsy have a worse prognosis and a high recurrence rate of SE. This outcome is not due to the SE itself, but related to the aetiology and type of epilepsy. The occurrence of SE is just an indicator of the severity of the disease.

Introduction

Although the mortality in recent years has declined considerably,[1-5] status epilepticus (SE) in children remains a medical emergency. Analyzing causes, risk factors, recurrence rate and outcome of SE in children with epilepsy may help to improve the immediate and long-term care for these children. Only a few studies on this subject have been published.[2 6 7] The Dutch Study of Epilepsy in Children (DSEC) is well suited to perform this type of analysis. We studied the occurrence of SE and the course after SE in our cohort of children with epilepsy. A comparison was made between children with and without SE.

Patients and methods

The prospective multicenter hospital-based DSEC started in 1988. After informed consent, we enrolled consecutively all children aged one month through 15 years who were referred between August 1988 and August 1992 because of a possible

unprovoked single seizure or epilepsy to one of the participating hospitals. At intake, 494 children suffered at least two or more unprovoked seizures or one unprovoked SE. SE was defined as a seizure with duration of at least 30 min or recurrent seizures lasting a total of more than 30 min without regaining consciousness in-between. We knew at that time that most children after a SE would be treated with antiepileptic drugs (AEDs) for at least some weeks to months. However, children who had ever used AEDs or started to use AEDs after the first seizure, had to be excluded from our first-seizure study according to its protocol.[8] This explains why children presenting with a solitary SE were not followed in the first seizure cohort, but in the cohort of children with new onset epilepsy, although they did not fully comply with the ILAE definition of epilepsy. Most children were referred directly by their general practitioner (51%) or by the paediatricians of the participating hospitals (25%). These paediatricians routinely referred all children with possible seizures to the departments of paediatric neurology. Some (16%), especially children with SE, were first seen in the emergency department. We excluded children with only febrile or acute symptomatic seizures, as they did not fulfill the requirements for the diagnosis of epilepsy, as well as children who were referred from other hospitals for a second opinion. The children were followed for five years. The mean age at intake of the total cohort (494) was 5.9 years (standard error (se) 0.2 years; median 5.5 years). Details have been described elsewhere.[9-11] We defined outcome in terms of terminal remission (TR): the interval from the last seizure (not the last SE!) to the end of follow-up at five years (TR5). TR5 was dichotomized (TR5<1 year, TR5>1 year). Besides, intractability was defined as a longest remission of less than three months during the last year of follow-up, despite adequate treatment.[11] Adequate treatment was defined as the optimal use of at least two AEDs.[12-14]

We studied the following factors for possible association with SE: aetiology, age, prior febrile seizures, classification of seizure type and epilepsy syndrome, and the results of prophylactic treatment with AEDs after the first SE. Results were compared with the few earlier studies on this subject. We used survival analysis to investigate the risk of a first SE and the risk of a first recurrence of SE during follow-up. These cumulative risks from the onset of epilepsy until the end of follow-up were displayed by means of Kaplan–Meier curves. Univariate logistic regression analysis was used to investigate which variables were associated with a first SE. To investigate which combination of independent variables was associated with SE before or at diagnosis, we performed a multivariate logistic regression analysis with a stepwise backward method (conditional). A variable was eliminated if its removal statistic had a probability greater than or equal to 0.10. We used simple parameter coding (each category of any particular variable was compared to the reference ca-

tegory of that variable). Odds ratios were calculated with 95% confidence intervals (CIs). All analyses were done using the SPSS statistical software.

Results

In the cohort, 47 out of 494 children had one or more episodes of SE. Figure 1 presents the cumulative risk of a first SE from the onset of epilepsy until the end of follow-up, and figure 2 the risk of at least one recurrence of SE.

Children with a first SE before or at inclusion

In the total cohort of 494 children, 41 (8.3%) had had one or more episodes of SE at the time the diagnosis of epilepsy was established, which was in fact the moment the children were included in the study (figure 3, table 1). Three children had febrile SE, followed by unprovoked seizures, and 38 unprovoked SE. In 32 children (71%), SE was the first seizure. Twenty-nine of them were on that occasion brought to the emergency room and included in the study. Three had had multiple episodes of SE before inclusion (one with complex partial SE). In nine children, the SE was not the first seizure, but the SE led to intake in our study. In five of them, SE was preceded by minor seizures like absences or complex partial seizures, which were recognized only when taking a thorough history at the intake in the study. Two had a tonic–clonic seizure and two a febrile seizure before SE.

During follow-up, 13 of the 41 (31.7%) children had one or more recurrences of SE. In the first three months, the recurrence rate was highest, later it dropped and remained stable over the years (figure 2). Eight children had one recurrent SE of which six had a TR5>1 year and two had a TR5<1 year. One child with two, one child with three and one child with six recurrences had a TR5<1 year; the other child with six recurrences died. The total number of SE of the child with complex partial SE was not exactly known. He had multiple SE before and after inclusion, but a TR5>1 year. Of the 28 children without recurrent SE, 18 (64.3%) had a TR5>1 year and eight (28.6%) had a TR5<1 year (of which two were intractable). One died and one was lost. Altogether, of the 41 children with SE before inclusion, two (4.9%) died. Thirteen (31.7%) had a TR5<1 year: 38.5% of those with recurrent SE versus 28.6% of those without recurrence. The 9.9% difference between these latter groups was not significant (95% CI: –21.4%; 41.2%). Six subjects never experienced another seizure or SE after intake. In four, the SE was their only epileptic seizure. The other two had had other seizures before intake: one had had one SE with fever and the other had had absences during six to 12 months ending in an absence status. Only these two started AED.

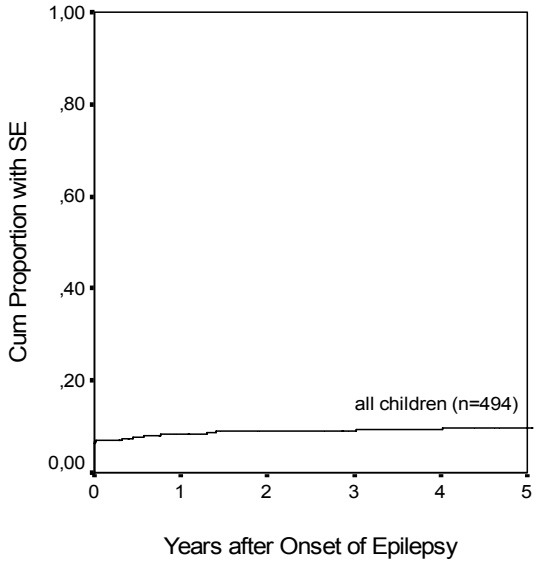

Figure 1. Cumulative risk of SE from the onset of epilepsy. Kaplan-Meier curve. T=0 is onset of epilepsy. Cases of SE before or at diagnosis are all listed as occurring at T=0.

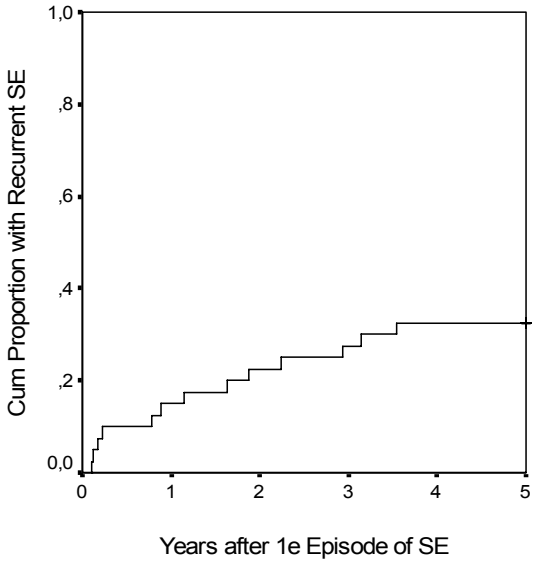

Figure 2. Cumulative risk of a first recurrence of SE during follow-up after the first episode of SE before or at the diagnosis of epilepsy. Kaplan-Meier curve. T=0 is time of first episode of SE; n=41.

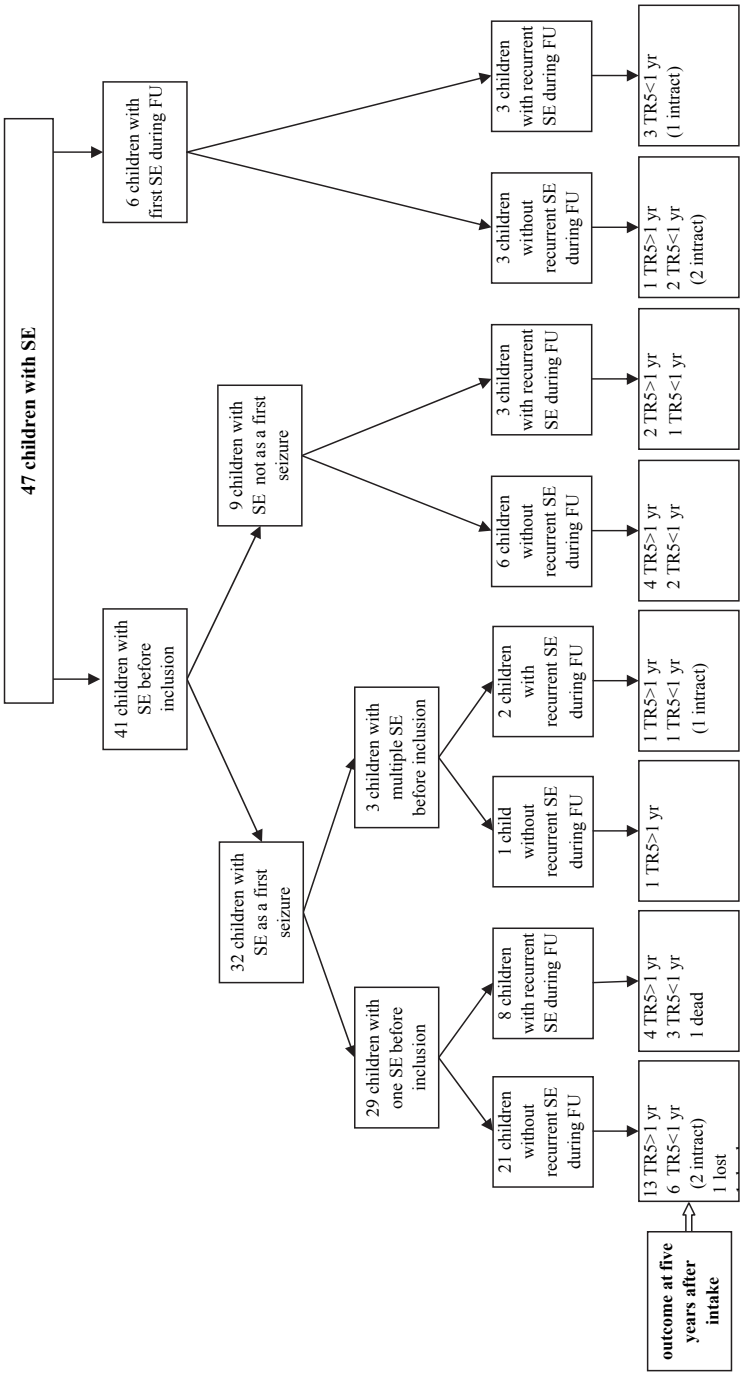

Figure 3. Forty-seven children with SE and their course and outcome.

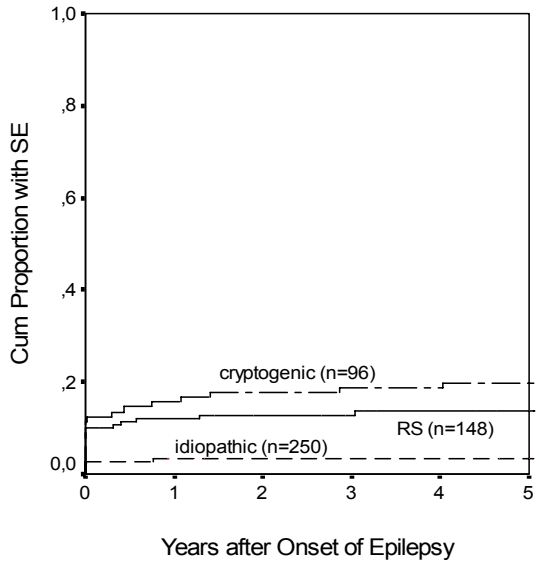

Figure 4. Cumulative risk of SE from onset of the epilepsy as a function of aetiology. Kaplan-Meier curve. T=0 is onset of epilepsy. Cases of SE before or at diagnosis are all listed as occurring at T=0. Log rank statistic: 26,07. Significance: <0.00001.

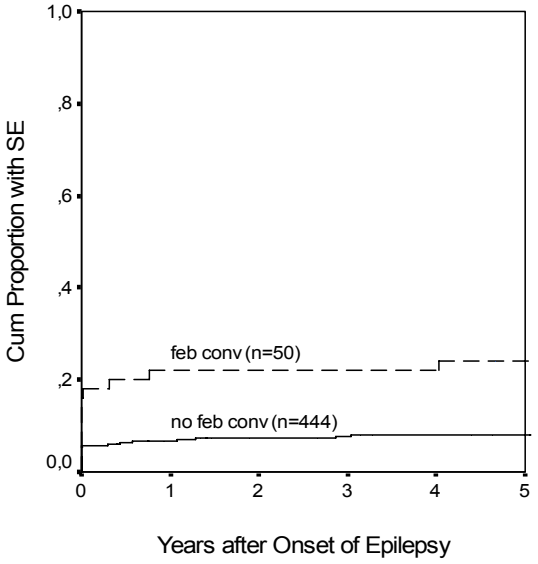

Figure 5. Cumulative risk of SE from onset of the epilepsy as a function of febrile seizures. Kaplan-Meier curve. T=0 is onset of epilepsy. Cases of SE before or at diagnosis are all listed as occurring at T=0. Log rank statistic:14,03. Significance: 0,0002.

Children with a first SE during follow-up

Six children (1.3%) had a first SE after the initial diagnosis of epilepsy (figure 3, and table 1); three within six months of follow-up (3.5, 4.4, and 5.3 months after inclusion), and three after more than one year of follow-up (14.7, 29.0, and 36.4 months). One child with two, one child with four and one child with five episodes of SE had a TR5<1 year. Three children had only one episode of SE: one had a TR5>1 year and the two with a TR5<1 year were intractable. Altogether, five of these six children had a TR5<1 year of which three were intractable.

Children without SE

Of the 447 children (table 1) without SE, 74.5% had a TR5>1 year, 21.2% had a TR5<1 year, of whom 29 (6.5%) were intractable; 2.7% was lost and 1.6% died. The difference in outcome between the 41 children with SE before inclusion (TR5<1 year: 31.7%) and the 447 children without SE (TR5<1 year 21.2%; 95% CI of the difference: –4.3%; 25.2%) was not significant.

Treatment

Nineteen of 41 children with a SE before inclusion were treated with AEDs within one week; 16 children started later. In ten, the indication for this was the occurrence of recurring seizure(s). Six children were never treated; none of them had recurrent SE and all had a TR5>1 year. Of the treated children, 54.3% had a TR5>1 year. As in the group without SE, the outcome was best in the group that responded well to the first AED. Treatment was not started earlier in the group with SE before intake as compared to the group without SE. Treatment delay was, perhaps unexpectedly, greatest in the small group of children with first SE during the follow-up, but this could be explained because two children were started on AEDs after two years of follow-up.

Recurrences

Fourteen of the 41 subjects had recurrent SE (one before and 13 after intake in the study): five before AEDs were started and nine after that time (table 2). Three out of these nine used only one AED and had their recurrent SE after AED withdrawal following a long remission (2) or as a result of poor compliance (1). Of the six who used more than one AED, three had their second SE after AED withdrawal after a long remission, and three during the period they used AED. In the latter three, change of AED could not prevent the occurrence of more seizures, although in only one a new SE occurred (TR5<1 year in two; TR5>1 year in one).

Table 1. Distribution of variables among children without SE, children with SE before inclusion, and children with a first SE after inclusion in the study.

	Children without SE	Children with SE before inclusion	Children with first SE after inclusion
Number (%)	447 (90.4%)	41 (8.3%)	6 (1.2%)
Male gender	216 (48.3)	20 (48.8)	3 (50.0)
Mean age at onset (yrs) (se; median)	5.6 (0.2; 5.3)	5.3 (0.6; 4.6)	4.0 (1.3; 3.1)
Mean interval between onset epilepsy and first visit (months) (se; median)	6.0 (0.5; 2.9)	3.5 (1.3; 0)	1.4 (0.8; 0.6)
Mean interval between onset epilepsy and start AED (months) (se; median)	2.1 (0.2; 0.7)	2.3 (0.9; 0.2)	7.8 (4.2; 2.7)***
Etiology		***	***
Idiopathic	242 (54.1)	8 (19.5)	0
Remote symptomatic/mental retardation	128 (28.6)	16 (39.0)	4 (66.7)
Cryptogenic	77 (17.2)	17 (41.5)	2 (33.3)
Preexisting neurological signs	59 (13.2)	9 (22.0)	3 (50.0) *
Mental retardation	94 (21.0)	10 (24.4)	4 (66.7) *
Classification epilepsy		***	***
Idiopathic generalized	198 (44.3)	6 (14.6)	0
Symptomatic generalized	38 (8.5)	1 (2.4)	2 (33.3)
Cryptogenic generalized	34 (7.6)	0	0
Idiopathic localization-related	30 (6.7)	0	0
Symptomatic localization-related	62 (13.9)	13 (31.7)	2 (33.3)
Cryptogenic localization-related	70 (15.7)	15 (36.6)	2 (33.3)
Other	12 (2.7)	6 (14.6)	0
Family history of epilepsy positive	54 (12.1)	3 (7.3)	1 (16.7)
Febrile seizures in history	38 (8.5)	12 (29.3) ***	0 ***
EEG at inclusion		***	***
Normal	119 (26.6)	3 (7.3)	1 (16.7)
Epileptiform discharges	267 (59.7)	22 (53.7)	1 (16.7)
Non-epileptiform abnormalities	55 (12.3)	16 (39.0)	3 (50.0)
no EEG	6 (1.3)	0	1 (16.7)
Treatment with AEDs			
None	84 (18.8)	6 (14.6)	0
Monotherapy	273 (61.1)	26 (63.4)	2 (33.3)
Polytherapy	90 (20.1)	9 (21.9)	4 (66.7)
Number of AEDs during follow-up			
0	68 (15.2)	6 (14.6)	0
1	208 (46.5)	15 (36.6)	0
>1	171 (38.3)	20 (48.8)	6 (100)
TR at 6 months		**	
6 months (no seizures)	129 (29.1)	22 (53.7)	0
Between 1 – 6 months	202 (45.5)	11 (26.8)	2 (33.3)
<1 months	113 (25.5)	8 (19.5)	4 (66.7)
TR at 12 months			
>6 months	265 (59.3)	25 (61.0)	1 (16.7)
<6 months	176 (39.4)	16 (39.0)	5 (83.3)
Lost/unknown	6 (1.3)	0	0
TR at 2 years			
>6 months	297 (66.4)	25 (61.0)	0
<6 months	128 (28.6)	13 (31.7)	6 (100.0)
Lost	6 (1.3)	1 (2.4)	0
Died	2 (0.4)	2 (4.9)	0
Unclear	14 (3.1)	0	0
TR at 5 years			**
>1 year	333 (74.5)	25 (61.0)	1 (16.7)
<1 year	95 (21.2)	13 (31.7)	5 (83.3)
Lost	12 (2.7)	1 (2.4)	0
Died	7 (1.6)	2 (4.9	
3-month remission during first 6 months	312 (69.8)	35 (85.4) *	0 ***
> 25 seizures during first 6 months	176 (39.4)	2 (4.9) ***	4 (66.7) ***

** p<0.05, ** p<0.01 *** p<0.001*

Table 2. Recurrent SE in 14 out of 41 patients with their first SE before intake.

Pat no.	Total no. of SEs	Moment of start AED	Moment of recurrence	No. of AEDs during follow-up	TR5
1	?	After all SE	Before AED	1	>1 yr
2	2	After all SE	Before AED	1	>1 yr
3	2	After all SE	Before AED	1	>1 yr
4	2	After 1st SE	After stop AED	1	>1 yr
5	2	After all SE	Before AED	1	<1 yr
6	2	After 1st SE	After stop AED	1	>1 yr
7	2	After all SE	Before AED	2	>1 yr
8	2	After 1st SE	After stop AED	2	>1 yr
9	2	After 1st SE	During AED treatment	4	<1 yr
10	2	After 1st SE	During AED treatment	5	>1 yr
11	3	After 1st SE	During AED treatment	2	<1 yr
12	4	After 1st SE	After stop AED	2	<1 yr
13	7	After 1st SE	After stop AED (poor compliance)	1	died
14	7	After 1st SE	After stop AED	4	<1 yr

Predictive variables

Table 1 shows the distribution of variables among children without SE, children with SE before inclusion, and children with a first SE after inclusion.

As compared to children without SE, children with SE before inclusion had less often idiopathic aetiology. Especially symptomatic and cryptogenic localization-related epilepsy were more frequent in the children with SE and idiopathic generalized epilepsy less frequent. A total of 29.3% of the children with SE before inclusion had a history of febrile seizures versus 8.5% of the children without SE. The EEG showed nonepileptiform abnormalities more often in children with SE before inclusion. During the first six months after inclusion, more than 50% was in remission compared to 30% of children without SE; 85% had at least three months of remission and only 5% had more than 25 seizures during the first six months of follow-up. For all of these seven variables, the difference between children with SE before inclusion and children without SE was statistically significant.

None of the six children with a first SE after inclusion had an idiopathic aetiology. They were more often mentally retarded and had more often pre-existing neurological signs. None had a history of febrile seizures. Like the children with SE before

Table 3. Outcome at five years follow-up (TR5) for each etiological group.

	Children without SE Number (%)	Children with SE before inclusion Number (%)	Children with first SE after inclusion Number (%)
Number (%)	447	41	6
Idiopathic			
TR at 5 years			
- >1 year	201 (83.0)	7 (87.5)	0
- <1 year	35 (14.4)	0	0
- lost	6 (2.5)	1 (12.5)	0
- died	0	0	0
Remote symptomatic			
TR at 5 years			
- >1 year	80 (62.5)	8 (50.0)	1 (25.0)
- <1 year	35 (27.4)	6 (37.6)	3 (75.0)
- lost	6 (4.7)	0	0
- died	7 (5.5)	2 (12.5)	0
Cryptogenic			
TR at 5 years			
- >1 year	52 (67.5)	10 (58.8)	0
- <1 year	25 (32.5)	7 (41.2)	2 (100)
- lost	0	0	0
- died	0	0	0

inclusion, the EEG showed more often non-epileptiform abnormalities. No child had a remission of three months during the first six months after inclusion, and 67% had more than 25 seizures. Only one child had a TR5>1 year, five had a TR5<1 year of which three were intractable. For all of the variables examined, including intractability, the difference between children with a first SE after inclusion and children without SE was significant, although the number of children with SE after intake was very small.

During five years of follow-up, two children with SE died. Both children had a SE as the first seizure. One child with Ohtahara syndrome had, apart from other seizures, seven episodes of SE until death, sometimes associated with fever. The compliance was poor and the child died after 4.8 years of follow-up due to pneumonia. The other child only had one SE and died after 1.5 years of follow-up because of an aspiration pneumonia not associated with a seizure. The mortality after five years of follow-up for children with SE was 4.3%, not significantly different from 1.6% of

children without SE (95% CI of the difference (2.7%): –3.4%; 10.0%).
We performed a multivariate analysis to investigate which combination of determinants was associated with SE at the time the diagnosis of epilepsy was established. Stepwise backward logistic regression analysis resulted in the selection of aetiology and febrile convulsions as statistically significant variables associated with SE before or at inclusion (figure 4 and 5). Odds ratios were 4.1 (95% CI 1.7; 10.1) for remote symptomatic versus idiopathic aetiology; 7.6 (95% CI 3.1; 18.7) for cryptogenic versus idiopathic aetiology; and 5.3 (95% CI 2.4; 11.9) for febrile seizures. The combination of history of febrile seizures with cryptogenic aetiology correlated best with SE. The poorest correlation with the occurrence of SE was found for the combination of idiopathic aetiology with the absence of febrile seizures.
None of the variables in table 1 was predictive of a recurrent SE in the univariate and multivariate analysis.

Discussion

In this hospital-based cohort study of 494 children with epilepsy, 47 children (9.5%) had one or more episodes of SE: 8.3% had had the first SE at the time the diagnosis of epilepsy was established. Other studies reported higher numbers of children with SE at the onset of epilepsy (Berg et al: 9.1%; Sillanpää: 20%).[2 7 15] The lower number at onset in our study can be explained partially by differences in the inclusion criteria. In the DSEC, we included only children with newly diagnosed untreated epilepsy to avoid a bias towards more severely affected epilepsy patients referred from other hospitals. Moreover, children with febrile seizures were included only if they also had had at least two unprovoked seizures or one unprovoked SE before the start of AED treatment. Consequently, children treated with AEDs after an acute symptomatic or febrile SE before the onset of epilepsy were not included in the DSEC. Sillanpää's study[2] counted 12 out of 30 children with provoked SE before the onset of epilepsy, Berg's[15] 11 out of 56 children and our study only three out of 41 children. Excluding these children, 7.7% in our study, 7.0% in Berg's study and 12% in Sillanpää's study had unprovoked SE before inclusion. The rate of SE during five years follow-up was also higher (8.2%) in the study of Berg[7] and Sillanpää[2] as compared to our study (3.8%). We found a strongly increased risk for SE during follow-up once a child had had SE before inclusion (31.7% vs. 1.2% for children without). In the study of Berg[7] these rates were 31.0% versus 5.9% at five years follow-up, and in the study of Sillanpää 51% versus 9.2%. Besides the already mentioned reasons, possible explanations for the still somewhat higher number of children with SE before and the markedly higher number after inclusion in the Fin-

nish study may be the different populations studied and use of different definitions of SE. Our study and the study by Berg concern incidence cohorts. The Finnish cohort consisted of children who developed epilepsy in the period 1961–1964, but these children were recruited retrospectively in 1972 and followed prospectively since then.[16] This may have caused a bias toward more severe patients. In the 1960s, treatment options with AEDs were limited and benzodiazepines for emergency treatment of seizures by the parents were not available. In the U.S.A., the FDA approved rectal diazepam gel in July 1997, the last year of inclusion in the study of Berg. However, these factors may not completely explain the variation between the studies.[7]

SE occurred most often at presentation of the epilepsy (figure 1). In 32 of 47 children (68%) with SE in our study, the SE was the first seizure (6.5% of all 494 children; 6.6% in Sillanpää's study and 4.1% for the children with unprovoked SE in Berg's study). Only 15 of 494 children (3.0%) had SE after a history of earlier short lasting seizures. Presentation of SE early in the course of epilepsy is in accordance with Sillanpää[2] and Berg.[15] In the follow-up study of Berg,[7] however, SE also occurred later during follow-up with a median time to first SE after initial diagnosis of epilepsy of 2.5 years.

Factors associated with the occurrence of SE were earlier SE, remote symptomatic (as in the studies of Berg[15] and Sillanpää[2]) or cryptogenic aetiology (as in the study of Berg[7]), and earlier febrile seizures (as in Sillanpää's study). In our study, after adjusting for epilepsy type or aetiology, there was no statistically significant difference in outcome between those with SE prior to intake and those without SE. This means that SE before intake per se has little impact on long-term outcome. The frequent remote symptomatic and cryptogenic aetiology in children with SE probably also explains the more frequent non-epileptiform abnormalities on EEG. The mean age of the children with SE in our study (5.1 years), especially of those with their first SE during follow-up, tended to be lower than that of children who presented without SE (5.6 years), but this difference was not significant. This was comparable to the findings of Berg.[7 15] They found at the beginning of their study, a younger age of onset of epilepsy in children with provoked and febrile SE (2.2 years), but not in children with unprovoked SE (5.4 years for children with unprovoked SE versus 5.9 years for children with epilepsy without SE). As in our study, children with SE during follow-up tended to be younger.[7] In the Finnish study, children with SE were significantly younger (2.8 years) than children with epilepsy without SE (5.2 years).[2] In this study many children had provoked SE, which may explain the younger age. Children with provoked SE have a younger age than children with unprovoked SE, and epilepsy also has an earlier onset after provoked

SE (Shinnar, Berg).[15 17]

Mortality was not significantly different between children with SE and without SE in our and Sillanpää's study. Both fatalities in our study were related to the underlying cause of the epilepsy. Berg found a higher mortality rate, but this was also entirely caused by the underlying neurological diseases and not by SE itself.[7]

The outcome of the epilepsy in our study, measured as TR5, was slightly, but not significantly, worse for children with SE before intake compared to children without SE. In the other studies, TR for children with SE also tended to be worse. In the Finnish study[18], after a follow-up of more than 30 years, fewer children with SE reached a TR of five years as compared to those without SE (RR 0.58; CI 0.34; 0.99; p=0.044). After adjusting for known significant variables like aetiology the difference was marginally significant (p=0.052) in multivariate analysis. However, the difference was statistically significant for children in remission without taking AEDs (risk ratio 0.50; 95% 0.26; 0.94; p=0.023). In the Finnish study, many children were included with SE after the moment of the diagnosis. In Berg's study,[7] children with initial SE were somewhat less likely to come into a terminal 3-year remission (48.1 vs. 62.2%; p=0.05), but not more frequently intractable. However, children with SE during follow-up had a lower remission rate and were more likely to be intractable. We agree with Berg that SE during follow-up simply means that the child still has severe and ongoing seizures, most often despite adequate therapy, and will therefore be less likely to go into remission.

Conclusions

All studies agree that SE is a common and serious presentation of epilepsy in children. Mostly SE occur at or prior to the diagnosis of epilepsy. It considerably enhances the risk for future SE. A trend exists for a shorter TR for children with SE. However, differences in prognosis in the three studies are not or only borderline significant. Symptomatic and cryptogenic localization-related epilepsy are much more frequent in children with SE, and are important negative factors determining the outcome of epilepsy. After adjusting for type of epilepsy and aetiology, SE is not significantly associated with a worse outcome any more. In our study, intractability is more common in children with the first SE after intake. However, SE is probably not the cause of intractability, but an indicator of the severity of the epilepsy in these children. No complete agreement exists on the importance of a history of febrile convulsions for the outcome and for the magnitude of the risk of SE in children without SE at presentation of epilepsy. Because of the high recurrence risk, parents of children who have had a SE should be instructed on how to

deal with a prolonged seizure and on the use of abortive medication.

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Chapter 8

General discussion

Diagnosis

The diagnoses seizure and epilepsy may be difficult in many cases. The diagnosis depends on the description of the event by an eyewitness and the interpretation of the description by the physician. A description of an event may be unclear because of insufficient observation, a lack of an eyewitness, a lack of capacity of the eyewitness to give a clear description or due to interpretations by the observer. The physician himself may misinterpret the account of the witness. A misdiagnosis may also be the consequence when physicians rely more on EEG findings than on clinical signs.[1-3] A misdiagnosis of epilepsy has many medical consequences like unnecessary investigations, prescription of AEDs which may have many side effects in childhood,[4 5] and psychosocial and socioeconomic consequences may occur also in childhood.[6] Unjustified rejection of the diagnosis epilepsy may also have disadvantages for the patient. It may even be fatal when, for example, a cardiac arrhythmia is overlooked as the cause for the spells.[7 8] In case of doubt however, a misdiagnosis of epilepsy does more harm for the patient than delaying the diagnosis for some time.[2 3] This is even more so in childhood. Children may be more susceptible for the adverse effects of AEDs.[4 5] Children do not drive cars, and they cannot loose their job. So for those children, who do not have frequent seizures, the need for treatment with AEDs may be less urgent than for adults.
In clinical and epidemiological studies on epilepsy without doubt patients are included with other paroxysmal disorders, and not all patients who do have epilepsy will be included. In most studies on prognosis and treatment of epilepsy the problem of diagnosing epilepsy (reliability and accuracy) and the inclusion of the correct patients is not mentioned. In this thesis the reliability and accuracy of several aspects of the diagnostic process are studied. The extent of this problem in daily practice and in studies, pitfalls and methods to reduce the amount of misdiagnoses are discussed in chapter 2.[3]

In chapter 3 we describe our study in which several paediatric neurologists had to diagnose one paroxysmal event.[9] The written description of the event was presented to them. In case they concluded the child suffered a seizure they had to classify the type of the seizure according the ILAE classification.[10] Using their clinical judgement, the individual observers only reached fair to moderate agreement on the diagnosis of a first seizure. The mean (SE) kappa was 0.41 (0.03). With use of defined descriptive criteria the mean kappa was 0.45 (0.03). After discussion between all participating paediatric neurologists the mean kappa for agreement increased to 0.60 (0.06), which is on the border of moderate to substantial for making a clinical

diagnosis. The agreement for the seizure classification by individual observers was only moderate (mean kappa 0.46) for clinical judgment, also when the criteria for diagnosis were used (kappa 0.57). After discussion within each panel the kappa between the two panels was substantial (0.69). Finally the results of all additional investigations were given. The panels succeeded only in a small minority of the children with a single seizure to make a specific syndrome diagnosis.
The paediatric neurologists in this study were experienced, and the criteria used for the diagnosis seizure increased the interrater agreement. In daily practice one would expect a lower interrater agreement.[11-15]

In chapter 4 the results are presented of our study on the accuracy of the diagnoses single seizure and epilepsy.[16 17] Children with the diagnosis epilepsy were followed for five years, children with a single seizure for at least two years. After two years follow-up the diagnosis of all these children was reassessed. Children with an unclear event were followed for one year to reassess whether new episodes might yield firm evidence for a definite diagnosis. After each new event the patient was re-evaluated and the diagnosis reconsidered. The definitions used in this section are explained in table 1a and 1b.
In none of the 170 children with a single seizure during the follow-up the diagnosis did prove to be wrong (false negative diagnosis in 0%, positive predictive value 100%). In four of the 54 children with a single unclear event, recurrent episodes enabled a definite diagnosis of epilepsy (false negative diagnosis in 7.4%; negative predictive value 92.6%). 170 out of 174 children with a single seizure were recognised at inclusion: sensitivity 97.7%.
In 412 of the 536 children seen with multiple events, an initial diagnosis of epilepsy was made. In 367 children the diagnosis was made on the history alone, in 45 children on the combination of the history and the results of the EEG. After follow-up, the initial diagnosis epilepsy was probably incorrect in 19 children (false positive diagnosis 4.6%; positive predictive value 95.4%). Seven of 124 children with multiple unclear episodes at intake later turned out to have epilepsy (false negative diagnosis 5.6%; negative predictive value 94.4%). 393 out of 400 children with epilepsy were diagnosed so at inclusion: sensitivity 98.3%. 117 of the 136 children without epilepsy were recognised at inclusion: specificity 86%.
For all 760 included children with one or more events the sensitivity was 98.1% and the specificity 89.8%.
In all children with uncertain events one or two EEG registrations were done. Several of these children had epileptiform discharges on the EEG. Three of the eight children with one unclear event and one of 27 children with multiple unclear

Table 1a. Definitions.

False positive diagnosis	Diagnosis epilepsy made in children without epilepsy: B
False negative diagnosis	Diagnosis no epilepsy in children who do have epilepsy: C
Sensitivity (true positive rate)	Percentage of al children with epilepsy recognized so at inclusion: (A)/(A+C)
Specificity (true negative rate)	Percentage of al children without epilepsy recognized so at inclusion: (D)/(B+D)
Positive predictive value	Percentage of children diagnosed with epilepsy at inclusion who really have epilepsy: (A)/(A+B)
Negative predictive value	Percentage of children diagnosed without epilepsy at inclusion who really don't have epilepsy: (D)/(C+D)

Table 1b. Diagnosis first seizure or epilepsy.

	after follow-up +	*after follow-up* -
at inclusion +	A	B
at inclusion -	C	D

events and an epileptiform EEG turned out to have epilepsy after follow-up of one year. The positive predictive value of the EEG in spells classified as unclear by experienced paediatric neurologists was 11.4%. This again confirms that the history of the events is most important to make a correct diagnosis.

Probably the rate of incorrect diagnoses has been underestimated in our study, since the diagnosis will not change if the child does not experience a recurrence of the events during follow-up. Moreover, the low false positive rate may be explained by the fact that the panel tended to prefer the diagnosis "unclear event" and not seizure or epilepsy in case of any doubt or disagreement between the panel members. In daily practice for most children these rigid diagnostics standards will not be applied, physicians may be less experienced and most children will not be discussed with more experienced physicians. All these factors explain in part the much higher rates of misdiagnosis in daily practice mentioned in the literature (chapter 2).[3 11-15] So one has to be careful to generalize the results from

this study to daily practice. On the other hand we can conclude that the results of the many studies done in the DSEC cohort are indeed very specific for children with epilepsy.

The electroencephalogram (EEG) is an important tool in the diagnosis of children with epilepsy. EEG findings are used for the classification of epileptic syndromes and may aid to determine the choice of the proper AEDs. The presence of epileptiform discharges is a strong predictor for the risk of recurrence after a first seizure.[16 18]

The reliability and accuracy determine the value of a diagnostic or prognostic tool. Data on the reliability of the visual interpretation of EEG-findings are scarce, however.[19-24]

In chapter 5 the interobserver reliability of the visual interpretation of the EEG in children with new-onset epilepsy is presented.[25] The interrater agreement was substantial for the interpretation of the EEG as normal or abnormal: mean (SE) kappa 0.66 (0.11); almost perfect for the presence of epileptiform discharges: mean kappa 0.83 (0.07); but moderate for abnormalities of the background pattern: mean kappa 0.53 (0.11); and only slight for the presence of focal non-epileptiform discharges: mean kappa 0.38 (0.13). After discussion with the participating neurophysiologists we defined non-epileptiform abnormalities as focal if they were restricted to a maximum of three adjacent electrodes. Using these definitions the agreement rates for the occurrence of an abnormal background-pattern improved from 0.53 to 0.73 (0.12), and for the occurrence of focal non-epileptiform abnormalities from 0.38 to 0.54 (0.14).

As the EEGs were described by experienced clinical neurophysiologists participating in studies on epilepsy, the reliability in this study will be expected to be better than in daily practice.[26 27]

Prognosis

The DSEC started the inclusion of children with a single unprovoked seizure several months earlier than the inclusion of the children with epilepsy.[16] In our study we tried to avoid systematic errors made in several earlier studies on first seizure.[18 28-38] In the earlier studies adult patients or children were included, but often also adults and children together. The latter does not make much sense as explained in the general introduction, unless children and adults are followed and analysed as separate groups. In our single seizure study the diagnosis was made unanimously by the panel of paediatric neurologists. The diagnosis was based on the history of

the event, interpreted with predefined descriptive criteria and it did not depend on EEG findings. Most children were included in the study soon after the seizure. The interval seizure to inclusion is of great importance because if any recurrences will occur they mostly do so soon after the first seizure. Every child had an EEG, which was performed as soon as possible after the seizure.[39] No child was treated after a single unprovoked seizure. Children with an uncertain diagnosis were also followed to test the accuracy of our inclusion criteria. Children with a single seizure were followed for two years. In most children with epilepsy treated with AEDs the drugs can be tapered after two years seizure freedom, and in some epilepsy syndromes even earlier. So, recurrences occurring more than two years after a single unprovoked seizure will not be of importance for the decision to start treatment. In chapter 6 the results are presented of our single seizure study.[16] After our study a few other studies on single seizures in childhood have been published.[40-44] Some of these publications concerned additional data of studies published before.[40 43] In comparison with the other studies the recurrence rate was in ours at the upper end of the range found in all studies.[45 46] In part this relatively high recurrence rate can be explained by the methodical differences.[16] Also in other studies no attention was paid to the accuracy of the diagnosis. We found that even for experienced paediatric neurologists diagnosing seizure(s) may be subject to error.[9 17] Only in our study no child was treated after a single seizure. Since our publications the diagnosis "uncertain event" or "unclassified paroxysmal events" has become more common in the literature.[2 9 15-17 44 47]

The first question after a single paroxysmal event has to be: how certain is the diagnosis? If the first question was answered "with a high probability it was an epileptic seizure", the second question will be: what is the chance of new seizures? Then the third question will follow: can new seizures be harmful for the child? And the last question is: will immediate treatment improve the prognosis for this child? When these facts are known, one has to balance the advantages and disadvantages of treatment with AED(s) for this child. We now know the probability of new seizures as well as the risk factors: remote symptomatic aetiology and epileptiform discharges on the EEG.[16 18] In the DSEC no child died due to the epilepsy itself.[16 48] In the study of Shinnar of 407 children with a mean follow-up of 14.2 years no children died due to the epilepsy as well.[49] In our own study, in which all children remained untreated after a single seizure, the long-term prognosis was very good for the majority of children.[16 17] In a study by Camfield, 31 children were randomised for treatment or placebo after a single seizure.[34] After one year, seven out of 17 (41%) untreated children were seizure free, and 10 out of 14 (71%) treated children. In four of the treated children the AED had to be stopped because of side

effects. So six children (42%) remained in the treated group without unacceptable side effects and without seizures. The advantage of lowering the number of children with continuing seizures was in this small study completely undone by the side effects of the AEDs. Fifteen years later the number of seizures was the same in both groups. Terminal remission (TR) rates of two years were achieved in 80% of the treated children and in 88% of the controls.[50 51] No other randomised studies have been done in children after a single seizure. Two randomised clinical trials including adults and children have been done without analysing the results separately.[37 41-43 52] Because of the many differences in epilepsy syndromes and of the side effects between adults and children this is not ideal. In the FIRST study, 27% of 419 patients was 2-16 years. In this study treatment after a single seizure reduced the recurrence rate from 42% to 24% after two years. However, starting treatment after the second seizure did not lower the TR rates of two years after three years follow-up (84% and 79%), nor the TR rates of five years after 10 years follow-up (64% in both groups).[37 43 52] No data on side effects were given. In the MESS study children and adults with a single seizure or a few infrequent seizures were randomised for treatment or placebo.[41] The age of 3.5% of patients was <5 years, 7,4% was 5-9 years, and 27% was 10-19 years. Of the patients with a single seizure 32% of the immediately treated patients had a recurrence and 39% of the patients with deferred treatment. Using these figures it would be necessary to treat 14 patients in order to prevent one single seizure recurrence within the first two years. For the high risk group (patients with an epileptiform EEG and remote symptomatic aetiology) the number to treat is five patients to prevent one seizure within the first year. At four, five and eight years follow-up no difference existed for the patients with a single seizure between immediate or delayed treatment: the TR rates of two years at five years follow-up were for both groups 92%, at eight years follow-up for immediate treatment 95% and for deferred treatment 96%. Of all included patients at five years follow-up 60% of the immediate treatment group and 41% of the deferred treatment group still used AEDs.[41] In the MESS study the two policies did not differ with respect to quality of life outcomes or serious complications. In a second paper the authors state that depending on social and psychological factors medication can be considered if the recurrence risk is relatively high (patients with an abnormal EEG or neurological deficits).[42] Treatment may however contribute to stigmatize the patient.[6]

We conclude that early treatment does not improve the long-term outcome of the epilepsy in terms of recurrence risk and development of intractable epilepsy. Few arguments exist to start treatment after a single unprovoked seizure in childhood. For most children time will learn if recurrences occur and with which frequency. In

case of doubt on the nature of the spells time may also clarify their nature. Moreover, part of the children with recurrences will turn out to have a benign syndrome like epilepsy with centrotemporal spikes. Although probably a significant number of children with benign epilepsy with centrotemporal spikes can be recognised after a single seizure due to the clinical signs of the seizure and the characteristic EEG, this will not be the case for all syndromes.[9 51] Even after a second seizure a specific syndrome will not be clear in a considerable number of children, or the syndrome can only be very broadly defined, or has to be revised during follow-up.[9 53-55] Even when neurologists in an epilepsy centre have to classify the seizure by videotape, a substantial variation in the classification exists. In contradiction with all other studies one claimed to be able to classify an epilepsy syndrome in 77% of patients presenting with a first seizure.[39] This is however in many aspects a curious study. Although the title suggests a study on first seizure, 45% of the included patients had earlier seizures. Seizures occurring in the setting of fever or sleep-deprivation were considered as unprovoked. Patients with a seizure due to earlier stroke, head injury, encephalitis, cancer and cerebral palsy, were excluded. Patients with an uncertain diagnosis were not mentioned. Also the inclusion criteria for age were curious: children were included, but only if aged five years or older (20% of included patients). No difference was made in analysis between the children and the adults. Seizures starting at the adult age are almost always of partial onset and of cryptogenic/symptomatic origin. Most syndrome diagnoses in this study were no specific diagnoses, but broadly defined diagnoses like idiopathic generalised epilepsy not further specified, or cryptogenic partial epilepsy.

Recommendations for evaluation and treatment have been published by the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society.[45 46] These Practice Parameters were based on the results of our and several other studies on single seizure in childhood. Routine EEG is recommended in these Practice Parameters, but other studies like neuroimaging and laboratory depend on specific clinical circumstances. Treatment with AEDs after a single seizure in childhood is not indicated to prevent epilepsy and will not improve prognosis. Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risk of pharmacological and psychosocial effects.[45 46] Studies published after the Practice Parameters didn't have any data that contradict these recommendations; on the contrary, they reinforced these recommendations.[6 15 41 42 44 47 49]

Status epilepticus (SE) is defined in most studies as seizures lasting for 30 minutes or longer. Nowadays there is much discussion about this definition. Once a seizure lasts for more than 5–10 minutes, it is unlikely to stop spontaneously within the next few minutes. Mechanisms that start seizures are different from inhibitory mechanisms. So there are probably two subcategories of children with epilepsy, one with short lasting seizures and the second one with a tendency to long lasting seizures.[56] Several studies have reported that, the longer a seizure lasts, the less likely it is to respond to abortive medication.[57-59] So it is nowadays recommended to administer medication after five minutes in an attempt to stop the seizure in an early stage. Several investigators propose to modify the definition of SE into a seizure lasting longer than five or 10 minutes.[57]

In the DSEC we investigated the incidence, causes and prognosis of SE in our cohort of children. We used the classical definition of 30 minutes. When the DSEC started it was the only existing definition. Moreover, other studies on incidence and prognosis of SE also used this definition. The results are presented in chapter 7.[60] Our results confirmed findings of the few other studies on this subject that SE is most frequent early in the course of epilepsy.[56 61-63] In our study in 71% of children with SE, an unprovoked SE was the first seizure they had. Children who suffered a SE had a much higher risk (32%) for future SE than children with short seizures as in the two other studies on this subject.[56 61] Children with SE had a trend to a slightly lower terminal remission rate. The difference was however not significant, in agreement with the other two studies. Intractability and mortality were not significantly higher either. Mortality was due to the underlying disease and not to the epilepsy in all studies. Most important for prognosis was not the duration of the seizure, but the aetiology.[60-63] An exception was the worse prognosis for children with SE after inclusion. However this is not due to SE: continuing seizures mean, by definition, a poor prognosis. As before, fast and adequate treatment for SE is of utmost importance.[58 59] Good instructions should be given verbally and in writing to the caregivers. They have to know how to act in case of recurrence and when to administer abortive medication by the rectal, buccal or nasal route. If the seizure continues for 10 minutes after the administration an ambulance has to be called. The occurrence of unprovoked SE itself does not influence the decision to prescribe AEDs. Again the benefits of reducing the risk of future seizures have to be balanced against the risk of pharmacological and psychosocial effects just like in all children with seizure(s). However, emotional factors may influence the decision, because SE is a very anxious and impressive experience for the parents.

In conclusion there is diagnostic uncertainty in a significant number of children with paroxysmal events. Moreover the prognosis of epilepsy is in most children not improved by early treatment. Treatment may have disadvantages, even if the diagnosis is certain. So the diagnostic process has to be done very carefully. AEDs should be prescribed only if the diagnosis is certain, and the advantages outweigh the disadvantages in the particular child.

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Summary:

Chapter 2 summarizes the problems in correctly making or rejecting the diagnosis of (a) seizure(s) and epilepsy. The diagnosis of a first seizure or epilepsy may be subject to interobserver variation and inaccuracy. This may have far-reaching consequences for the patients involved. We reviewed in this chapter the current literature. Studies on the interobserver variation of the diagnosis of a first seizure show that such a diagnosis is subject to considerable interobserver disagreement. Interpretation of the electroencephalogram (EEG) findings is also subject to interobserver disagreement and is influenced by the threshold of the reader to classify EEG findings as epileptiform. The accuracy of the diagnosis of epilepsy varies from a misdiagnosis rate of 5% in the prospective DSEC, in which the diagnosis was made by a panel of three experienced paediatric neurologists, to at least 23% in a British population-based study, and may be even higher in everyday practice. The level of experience of the treating physician plays an important role. The EEG may be helpful but one should be reluctant to make a diagnosis of epilepsy mainly on the EEG findings without a reasonable clinical suspicion based on the history. Being aware of the possible interobserver variation and inaccuracy, adopting a systematic approach to the diagnostic process, and timely referral to specialized care may be helpful to prevent the misdiagnosis of epilepsy.

In chapter 3 we assessed the interrater agreement of the diagnosis and the classification of a first paroxysmal event in childhood. The descriptions of 100 first paroxysmal events were submitted to two panels each consisting of three experienced paediatric neurologists. Each observer independently made a diagnosis based on clinical judgment and thereafter a diagnosis based on predefined descriptive criteria. Then, the observers discussed all patients within their panel. The agreement between the six individual observers was assessed before discussion within each panel and after that, between the two panels.
Using their clinical judgement, the individual observers reached only fair to moderate agreement on the diagnosis of a first seizure: mean (SE) kappa 0.41 (0.03). With use of defined descriptive criteria the mean SE kappa was 0.45 (0.03). The kappa for agreement between both panels after intra-panel discussion increased to 0.60 (0.06). The mean kappa for the seizure classification by individual observers was 0.46 (0.02) for clinical judgment and 0.57 (0.03) with use of criteria. After discussion within each panel the kappa between the panels was 0.69 (0.06). In 24 out of 51 children considered to have had a seizure, agreement was reached between the

panels on a syndrome diagnosis. However, the epileptic syndromes were in most cases only broadly defined.
In conclusion the interrater agreement on the diagnosis of a first seizure in childhood is only moderate. This phenomenon hampers the interpretation of studies on first seizures in which the diagnosis is only made by one observer. The use of a panel increased the interrater agreement considerably. This approach is recommended at least for research purposes. Classification into clinically relevant syndromes is possible only in a minority of children with a single seizure.

In chapter 4 we assessed the accuracy of the diagnosis of epileptic seizures in children. 881 children were referred to the Dutch Study of Epilepsy in Childhood because of possible seizures. We based the diagnosis in these children on predefined descriptive criteria, as applied by a panel of three paediatric neurologists. Children with a definite other diagnosis were excluded in the DSEC. All children with unclear events were followed up for one year and children with seizures were followed up for two years to assess the accuracy of the diagnosis.
In 170 of 224 children seen after a single event, the incident was classified initially as an epileptic seizure, and in 54 as an unclear event. In none of the 170 children did during the follow-up the diagnosis proved to be wrong. In four of the 54 children, recurrent episodes enabled a definite diagnosis of epilepsy. In 412 of the 536 children seen with multiple events, an initial diagnosis of epilepsy was made. After follow-up, this initial diagnosis was probably incorrect in 19. In contrast, seven of 124 children with multiple unclear episodes at intake later received the diagnosis epilepsy. So the rate of a false positive diagnosis of an epileptic seizure was 0%, the positive predicting value 100%, the sensitivity 97.7% and the negative predicting value 92.6%.
In this cohort a false positive diagnosis of epilepsy was made in 4.6% of the children initially diagnosed with epilepsy. A definite diagnosis of epilepsy or seizure was delayed in 5.6% of children initially diagnosed with multiple unclear events and in 7.4% of children with one unclear event.
In the 35 children who according to the judgement of the panel had an unclear event, but an epileptiform EEG, only a small minority of four children turned out to have epilepsy during follow-up.
Probably the rate of incorrect diagnoses will be underestimated in this study, since the diagnosis will not change if the child does not experience a recurrence of the events during follow-up. Moreover, the low false positive rate may be explained by the fact that the panel tended to prefer the diagnosis unclear event and not seizure or epilepsy in case of any doubt or disagreement between the panel members.

In daily practice for most children these rigid diagnostic standards will not be applied, many children will not be discussed with others, and physicians may be less experienced. All these factors explain in part the much higher rates of misdiagnosis in daily practice mentioned in the literature (chapter 2).

In chapter 5 the role of the EEG in the diagnostic process is discussed and the reliability of visual interpretation of electroencephalograms (EEG) investigated. The reliability is of great importance in assessing the value of a diagnostic tool. We prospectively obtained 50 standard EEGs and 61 EEGs after partial sleep deprivation from 93 children (56 males, 37 females) with a mean age of six years 10 months (SE 5mo; range 4mo–15y 7mo) with one or more newly diagnosed, unprovoked seizures. Two clinical neurophysiologists independently classified the background pattern and the presence of epileptiform discharges or focal non-epileptiform abnormalities of each EEG. The agreement was substantial for the interpretation of the EEG as normal or abnormal (kappa 0.66), and almost perfect for the presence of epileptiform discharges (kappa 0.83). The agreement for the occurrence of an abnormal background pattern and focal non-epileptiform discharges was initially only fair to moderate. After defining these disturbances the agreement was improved to kappa's of 0.73 and 0.54 (moderate to substantial). In conclusion, the reliability of the visual interpretation of EEGs in children is for the most important finding, the presence of epileptiform abnormalities, almost perfect.

In chapter 6 we assessed the accuracy of the diagnosis of a first unprovoked seizure in childhood, the recurrence rate within two years, the risk factors for recurrence, and the outcome at two years after recurrence. One hundred and fifty six children aged one month to 16 years after a first seizure, and 51 children with a single unclear event were followed up. The diagnosis of a seizure was confirmed by a panel of three child neurologists on the basis of predefined diagnostic criteria. None of the children was treated after the first episode.
Five out of 51 children with an unclear event developed epileptic seizures during one year follow up. The diagnosis did not have to be revised in any of the 156 children with a first seizure during two years follow-up. The overall recurrence rate after two years was 54%. Significant risk factors were an epileptiform EEG (recurrence rate 71%) and remote symptomatic aetiology and/or mental retardation (recurrence rate 74%). For the 85 children with one or more recurrences, terminal remission irrespective of treatment two years after the first recurrence was >12 months in 50 (59%), <six months in 22 (26%), six to 12 months in 11 (13%) and unknown in two (2%). Taking the no recurrence and recurrence groups together,

a terminal remission of at least 12 months was present in 121 out of the 156 children (78%).
The diagnosis of a first seizure can be made accurately with the help of strict diagnostic criteria. The use of these criteria may have contributed to the rather high risk of recurrence in this series. However, the overall prognosis for a child presenting with a single seizure is very good, even if treatment with antiepileptic drugs is not immediately instituted.

In chapter 7 we studied the course and outcome of epilepsy in children having had a status epilepticus (SE) as the presenting sign or after the diagnosis.
A total of 494 children with newly diagnosed epilepsy, aged one month through 15 years, were followed prospectively for five years. A total of 47 out of these 494 children had SE. Forty-one of them had SE when epilepsy was diagnosed. For 32 (78%), SE was the first seizure. SE recurred in 13 out of 41 (32%). Terminal remission at five years (TR5) was not significantly worse for these 41 children: 31.7% had a TR5 <1 year versus 21.2% of 447 children without SE. They were not more often intractable. Five out of six children with first SE after diagnosis had a TR5 <1 year. Mortality was not significantly increased for children with SE. Independent factors associated with SE at presentation were remote symptomatic and cryptogenic aetiology, and a history of febrile seizures. Children with first SE after inclusion more often had symptomatic aetiology. Although we found a trend for shorter TR5 in children with SE at presentation, outcome and mortality were not significantly worse. Aetiology is an important factor for the prognosis. Children with SE during the course of their epilepsy have a worse prognosis and a high recurrence rate of SE. This outcome is not due to the SE itself, but related to the aetiology and type of epilepsy. The occurrence of SE is just an indicator of the severity of the disease.

Samenvatting en discussie

Inleiding

Epilepsie is een aandoening waarbij patiënten gedurende een deel van hun leven bij herhaling epileptische aanvallen doormaken. De epileptische aanvallen zijn het symptoom van de onderliggende ziekte, de epilepsie. De aanvallen moeten zonder directe aanleiding optreden. Indien epileptische aanvallen wel een directe (acute) oorzaak hebben, zoals aanvallen tijdens koorts bij jonge kinderen (koortsstuipen), aanvallen door een te laag bloedsuiker of aanvallen tijdens een hersenvliesontsteking, spreekt men niet van epilepsie. Dergelijke aanvallen worden acuut symptomatische insulten genoemd. Reden van onderscheid is dat acuut symptomatische aanvallen optreden onder bijzondere omstandigheden, en er geen sprake is van een chronische aandoening. Overigens kan een dergelijke omstandigheid, zoals een hersenvliesontsteking of ernstige hersenschudding, bij een deel van deze patienten blijvend hersenletsel tot gevolg hebben. Sommige van deze patiënten blijken daardoor later alsnog epilepsie te ontwikkelen. Deze wordt dan "laat symptomatische epilepsie" genoemd. Tijdens een epileptische aanval is er een overmatige elektrische activiteit in de hersenen, wat het makkelijkste is te omschrijven als een soort kortsluiting of onweersbui. De verschijnselen tijdens een aanval kunnen van patiënt tot patiënt sterk verschillen. Dit wordt bepaald door de locatie waar de overmatige activiteit in de hersenen plaats vindt en de leeftijd van de patiënt. Bij partiele aanvallen beperkt de ontlading zich tot een gedeelte in de hersenen, bij gegeneraliseerde aanvallen vindt de ontlading overal in de hersenen plaats. In tabel 1 staat de grove indeling van de aanvalstypen. Zowel binnen de groep gegeneraliseerde als binnen de groep partiele aanvallen kan een groot aantal subtypen worden onderscheiden. Het streven is de aanvallen zo nauwkeurig mogelijk te classificeren.

In de westerse wereld ontstaat ongeveer bij acht per 10.000 (0.08%) mensen per jaar epilepsie (incidentie). 0.6% van de westerse bevolking heeft op dit moment epilepsie (prevalentie). De kans epilepsie te krijgen is verreweg het grootste op de kinderleeftijd. Bij 75% van alle patiënten begint de epilepsie voor het twintigste jaar, en meestal al op zeer jonge leeftijd. Bij bejaarden neemt de kans op epilepsie echter weer toe. De epilepsie is dan een gevolg van een verworven hersenaandoening (laat symptomatische epilepsie) zoals een doorgemaakte beroerte (CVA).

Op de kinderleeftijd vindt nog een enorme rijping plaats van de hersenen. De functie van de hersenen verandert met de leeftijd. Epileptische aanvallen heb-

Tabel 1. Grove classificatie van epileptische aanvallen.

Aanvalstype		*Fysiologie*	*Verschijnselen tijdens aanval*
Partieel	Eenvoudig partieel	Ontlading in een klein deel van de hersenen.	Patiënt blijft bij kennis, ervaart psychische of lichamelijke verschijnselen en maakt de aanval bewust door.
Partieel	Complex partieel	Ontlading in een groter deel van de hersenen.	Patiënt reageert niet meer op omgeving en kan zich achteraf niets herinneren van de aanval. Omstanders kunnen onwillekeurige handelingen waarnemen.
Gegeneraliseerd	Tonisch-clonisch	Ontlading in de gehele hersenen	Bewusteloosheid gedurende één tot enkele minuten, heftige spierschokken, soms tongbeet en urineverlies.
Gegeneraliseerd	Absence	Ontlading in de gehele hersenen.	Gedurende 5-15 seconden plots staren en niet reageren op de omgeving. Meestal tientallen malen per dag.

ben daardoor op verschillende leeftijden een zeer verschillende symptomatologie. Zozeer dat diverse aanvalstypen zelfs alleen in bepaalde leeftijdsfasen worden gezien. Door de nog voortgaande rijping van de hersenen kunnen de symptomen van de aanvallen veranderen tijdens het opgroeien van het kind. Ook is door deze rijping bij kinderen de epilepsie vaker een tijdelijk verschijnsel dan op volwassen leeftijd. De oorzaken van epilepsie zijn bij kinderen en volwassenen grotendeels verschillend. Veelal is de epilepsie bij kinderen bepaald door erfelijke aanleg (idiopathische epilepsie). De epilepsie kan ook een gevolg zijn van aangeboren afwijkingen in de hersenen, chromosomale afwijkingen, complicaties bij de bevalling en soms van stofwisselingsziekten in de hersenen (laat symptomatische epilepsie). De oorzaak kan ook onbekend blijven (cryptogene epilepsie). Epilepsie ontstaan op volwassen leeftijd is meestal een gevolg van een verworven hersenaandoening, zoals epilepsie na een ernstig hersenletsel door een ongeval, na een beroerte, of door een tumor (laat symptomatische epilepsie). Er zijn dus verschillende soorten epileptische aanvallen en vele verschillende aandoeningen (epilepsiesyndromen) waarbij epileptische aanvallen optreden. Een grove indeling van de epilepsiesyndromen staat in tabel 2.

Tabel 2. Grove indeling van epilepsiesyndromen.

Oorzaak	Idiopathisch	Laat symptomatisch	Cryptogeen
Aanvalstype			
Partieel	Idiopathische locatiegebonden epilepsie	Locatiegebonden symptomatische epilepsie	Locatiegebonden cryptogene epilepsie
Gegeneraliseerd	Idiopathische gegeneraliseerde epilepsie	Gegeneraliseerde symptomatische epilepsie	Gegeneraliseerde cryptogene epilepsie

Patiënten met idiopathische epilepsie hebben geen of weinig andere klachten naast de aanvallen. Laat symptomatische epilepsie is een gevolg van een neurologische ziekte en zal vaak wel met andere ziekteverschijnselen gepaard gaan. Binnen alle zes grote groepen genoemd in tabel 2 zijn weer zeer vele meer specifieke syndromen te onderscheiden. De juveniele myoclonus epilepsie (JME) bijvoorbeeld valt in de categorie idiopathische gegeneraliseerde epilepsie; benigne (goedaardige) epilepsie met centrotemporale pieken ofwel benigne rolandische epilepsie in de categorie idiopathische locatiegebonden epilepsie. JME begint in de puberteit, patiënten hebben tonisch-clonische aanvallen, absences en myoclonieen (gedurende hoogstens enkele seconden spierschokken). Vaak treden de aanvallen op kort na het ontwaken. De aanvallen bij JME kunnen worden uitgelokt door factoren als stress, slaaptekort, alcoholgebruik, of lichtprikkels (stroboscoop in de disco). Slechts een klein deel van de beschikbare medicijnen tegen epilepsie (AEDs) is bij JME werkzaam. Als het juiste AED wordt gebruikt is de patiënt meestal aanvalsvrij. JME gaat echter niet over zodat de medicatie het gehele leven gebruikt moet worden. Benigne rolandische epilepsie komt voor bij schoolkinderen, dus juist voor de puberteit. De aanvallen zijn partieel, kinderen kunnen tijdens een aanval niet praten, maken vreemde gorgelgeluiden en kwijlen, maar blijven wel bij kennis. De aanvallen kunnen bij een minderheid ook tonisch-clonisch verlopen. De meeste kinderen hebben maar weinig aanvallen, die bij het merendeel alleen tijdens de slaap optreden. Rolandische epilepsie gaat altijd weer over, uiterlijk in de puberteit. Behandeling met AEDs is bij het merendeel van deze kinderen niet nodig gezien de lage aanvalsfrequente, het nachtelijke optreden en het tijdelijke karakter van deze aandoening. Deze twee voorbeelden maken duidelijk dat een nauwkeurige classificatie van aanvalstype en epilepsiesyndroom van zeer groot belang is. Al-

leen dan kan een prognose worden gegeven van het beloop, kan beter worden afgewogen of behandeling met AEDs is gewenst, en zo ja welke van de vele AEDs geschikt zijn voor deze patiënt, hoe lang moet worden behandeld en of verder onderzoek noodzakelijk is. In de praktijk is het helaas niet bij alle patiënten mogelijk het epilepsiesyndroom nauwkeurig te classificeren.
De consequenties van epilepsie kunnen voor kinderen en volwassenen verschillend zijn. Volwassenen worden beperkt in de verkeersdeelname (rijbewijs), hun werk, sociale activiteiten, enzovoort. Daarnaast zijn de bijwerkingen van de medicijnen verschillend afhankelijk van de leeftijd. Denk bijvoorbeeld aan de schadelijke effecten die kunnen optreden bij het gebruik tijdens zwangerschap voor het ongeboren kind. Kinderen zijn vaak weer meer gevoelig voor bijwerkingen op het gedrag en de cognitie. De noodzaak van behandeling met AEDs kan bij kinderen minder groot zijn.
Gezien de andere symptomatologie, het verschillend beloop, de verschillende oorzaken en de gevolgen voor de patiënt is het wenselijk bij behandeling en in wetenschappelijke onderzoeken een onderscheid te maken tussen epilepsie bij kinderen en volwassenen. Merkwaardig genoeg wordt nog steeds in veel onderzoeken dit onderscheid niet gemaakt.
Over het natuurlijke beloop van epilepsie zijn slechts beperkte gegevens bekend doordat bijna alle patiënten worden behandeld met AEDs, vaak al na één aanval. Daarnaast wordt veel onderzoek verricht in gespecialiseerde ziekenhuizen. Daar worden echter vooral patiënten met de ernstigere vormen van epilepsie naar verwezen. Hierdoor kan in onderzoeken een vertekend beeld optreden van het beloop van epilepsie. Ruwweg lijkt het zo dat van de patiënten die worden behandeld met medicijnen ongeveer 75% geen aanvallen heeft. Een kleine minderheid van de kinderen heeft frequent aanvallen die niet met medicijnen zijn te behandelen. Hierdoor kan de kwaliteit van leven zeer nadelig worden beïnvloed en de cognitieve ontwikkeling worden geschaad.

Dutch Study of Epilepsy in Childhood (DSEC)

In 1988 besloten de kinderneurologen Willem Frans Arts, Oebo Brouwer, Boudewijn Peters en Hans Stroink, de neuroloog Cees van Donselaar en de epidemioloog Ada Geerts een onderzoeksgroep op te richten. Aanvankelijk droeg het onderzoek de naam Zuid-Hollands Kinderepilepsie Onderzoek (ZHKO), later omgedoopt tot Dutch Study of Epilepsy in Childhood (DSEC). Om de eerder genoemde bezwaren te ondervangen werden in dit onderzoek alleen kinderen met de leeftijd van één maand tot 16 jaar geïncludeerd met nieuw ontstane epilepsie of een eenmalige

epileptische aanval. Aanvallen in de eerste levensmaand zijn veelal acuut symptomatisch en worden in onderzoeken naar epilepsie niet betrokken. In de periode augustus 1988 tot augustus 1992 werden alle kinderen aangemeld met niet acuut symptomatische epileptische aanvallen verwezen naar de deelnemende ziekenhuizen, alsmede kinderen waarbij de diagnose werd overwogen maar niet zeker was. Kinderen eerder behandeld met AEDs, alsmede kinderen verwezen vanuit andere ziekenhuizen werden niet geïncludeerd. De deelnemende ziekenhuizen waren het Westeinde Ziekenhuis en het Juliana Kinderziekenhuis in Den Haag, het Academisch Ziekenhuis Leiden en het Academisch Ziekenhuis Rotterdam. Dit laatste ziekenhuis had twee locaties: het Dijkzigt Ziekenhuis en het Sophia Kinderziekenhuis. Van alle kinderen werden de gegevens zorgvuldig vastgelegd zoals de symptomen van de aanvallen, de medische voorgeschiedenis, het al dan niet voorkomen van epilepsie in de familie en het lichamelijk neurologische onderzoek. Bij alle kinderen werd een EEG (hersenfilmpje) gemaakt, en wanneer dit geen afwijkingen liet zien volgde een tweede EEG zo mogelijk tijdens slaap. Bij de meeste kinderen werd een scan van de hersenen gemaakt, en ander onderzoek als de behandelend kinderneuroloog dit noodzakelijk achtte. Alle aangemelde kinderen werden besproken in een panel bestaande uit drie van de vier deelnemende kinderneurologen; de behandelend kinderneuroloog nam niet deel aan het bespreken van zijn eigen patiënten. In eerste instantie werd de diagnose gesteld op grond van de aanvalsbeschrijving, zonder kennis van het aanvullend onderzoek, waaronder het EEG. Alleen bij kinderen met meerdere aanvallen mocht het EEG in geval van twijfel worden meegewogen in de diagnose wel of niet epilepsie. Door deze besprekingen in een panel hoopten we de diagnose zo nauwkeurig mogelijk te stellen, zodat we zo weinig mogelijk kinderen zouden missen met epileptische aanvallen en zo weinig mogelijk kinderen te includeren met niet epileptische aanvallen. Er werden in de DSEC 760 kinderen geïncludeerd: 170 met één epileptische aanval, 412 met epilepsie, 54 met één en 124 met meerdere aanvallen zonder diagnose (onduidelijke aanvallen). Dit betekent dat ongeveer 75% van alle kinderen met epilepsie in de regio van de deelnemende ziekenhuizen is geïncludeerd. Kinderen met aanvallen waarvan het panel meende dat ze niet epileptisch waren, maar waarvoor ook geen andere verklaring voorhanden was, werden één jaar vervolgd. Kinderen met één epileptische aanval kregen geen AEDs voorgeschreven en werden twee jaar vervolgd. Als er echter nieuwe aanvallen optraden werden zij vervolgd in het onderzoek van de kinderen met epilepsie. De kinderen met epilepsie (meerdere epileptische aanvallen) werden aanvankelijk vijf jaar vervolgd. Later werd besloten de studieduur te verlengen en deze kinderen 15 jaar te vervolgen. Het al dan voorschrijven van AEDs was ter beoordeling van de behandelend

kinderneuroloog in overleg met de ouders en het kind. Tijdens het vervolgen van de kinderen werd niet alleen gekeken hoe het ziektebeloop was, maar ook of de diagnose gesteld op moment van inclusie juist bleef.
In de DSEC was zo een bijzondere en grote groep kinderen bijeen gebracht met niet eerder behandelde epileptische aanvallen die langdurig kon worden vervolgd. Er waren diverse vraagstellingen in de DSEC. Een groot deel van de onderzoeksresultaten is elders gepubliceerd: cognitie en gedrag bij kinderen met epilepsie; "quality of life" (invloed van de aandoening en de behandeling op het algehele welbevinden en functioneren); sterfte bij kinderen met epilepsie; de aanvullende waarde van een tweede EEG tijdens slaap; relatie tussen de behandelduur met AEDs en de kans op succesvol staken van deze medicatie; de mate waarin de epilepsie familiair voorkomt; het al dan niet bestaan van immunologische afwijkingen (stoornissen in het afweersysteem) als oorzaak van de epilepsie of juist als gevolg van de behandeling; het voorspellen van het beloop van de aandoening vroeg na het stellen van de diagnose: is de epilepsie makkelijk te behandelen en/of tijdelijk, of juist zeer slecht behandelbaar en/of chronisch. Deze publicaties staan vermeld in de publicatielijst DSEC.
In dit proefschrift komen de volgende onderwerpen aan de orde: de nauwkeurigheid en betrouwbaarheid van de diagnose één epileptische aanval; het beloop na één epileptische aanval (hoeveel kinderen ontwikkelen epilepsie, is dit te voorspellen en is de eventuele epilepsie al dan niet ernstig); de nauwkeurigheid en betrouwbaarheid van de diagnose epilepsie; de nauwkeurigheid en betrouwbaarheid van de beoordeling van het EEG; hoe vaak komt een zeer langdurige epilepsieaanval (status epilepticus) voor en wat betekent dit voor het verdere beloop van de aandoening; praktische adviezen voor de diagnostiek en het al dan niet starten van een behandeling met AEDs.

Hoofdstuk 2

In hoofdstuk 2 wordt de problematiek rond het stellen van de diagnose besproken. Op de kinderleeftijd komt een zeer groot en divers scala voor van aanvalsgewijs verlopende aandoeningen. De diagnose berust op de omschrijving van de aanvallen door getuigen. Deze beschrijving kan ontbreken doordat tijdens de aanval niemand aanwezig was, onduidelijk zijn doordat de omstander(s) in paniek raakten, zij de gebeurtenis niet goed kunnen verwoorden of zij zelf de aanval interpreteren in plaats van te beschrijven. Ook de arts kan de gegevens onjuist interpreteren. Bij het stellen van de diagnose spelen derhalve vele subjectieve factoren een rol. Bij het stellen van de diagnose zal daarom een zekere mate van onzekerheid bestaan.

Ook wordt de diagnose nogal eens op grond van aanvullend onderzoek gesteld, en dan met name op EEG uitslag, in plaats van op de beschrijving van de aanvallen (zie hoofdstuk 5). In Groot-Brittannië wordt naar aanleiding van een rechtszaak, aanhangig gemaakt door ouders bij wie een kind ten onrechte werd behandeld voor epilepsie, verondersteld dat bij ruim 30% van de kinderen met epilepsie de diagnose onjuist is. Ook wordt in Groot-Brittannië een groot deel van de kinderen die wel epilepsie hebben "overbehandeld", dat wil zeggen met te veel medicijnen of in te hoge doseringen. Het betreft daarom een groot praktisch probleem. In dit hoofdstuk worden een aantal adviezen gegeven om onjuiste diagnoses zoveel mogelijk te voorkomen. Wij menen dat het voor kinderen en volwassenen minder schadelijk is de diagnose epilepsie in een wat later stadium te stellen dan vroegtijdig deze diagnose (onjuist) te stellen op grond van onvoldoende gegevens. Het gevolg bij een verkeerde diagnose is onnodig behandelen, vaak met veel AEDs in hoge doseringen omdat de AEDs niet zullen helpen, onnodig onderzoek, sociale beperkingen en stigmatisering van patiënten die geen epilepsie hebben. Bovendien verbetert vroege behandeling de prognose van epilepsie niet. Dit laatste komt later nog uitgebreid aan de orde. Bij het stellen van diagnoses bij patiënten met onduidelijke aanvallen heeft een conservatieve benadering sterk de voorkeur. Men dient wel op zijn hoede te zijn dat aanvallen ook door een hartritmestoornis kunnen worden veroorzaakt. Dit is een van de weinige alternatieve diagnoses die ernstige consequenties heeft.

Hoofdstuk 3

In hoofdstuk 3 wordt beschreven in hoeverre kinderneurologen het onderling eens zijn of er al dan niet sprake is geweest van een epileptische aanval (reliability). Wij onderzochten bij 100 kinderen met één doorgemaakte aanval of zes kinderneurologen het al dan niet met elkaar eens waren over de aard van de aanval: wel of niet een epileptische aanval. In de geneeskunde spelen bij alle oordelen subjectieve factoren mede een rol en daarom zal er nooit een volledige 100% overeenstemming bestaan tussen het oordeel van verschillende artsen. De mate van overeenstemming kan met hulp van een formule in getal worden uitgedrukt. Deze maat is de kappa. Een kappa van nul betekent dat de mate van overeenstemming tussen verschillende beoordelaars op puur toeval berust. Met het gooien van dobbelstenen of door domweg zonder enige kennis te raden zal men hetzelfde resultaat bereiken. Een kappa van -1.0 betekent volledige onenigheid; een kappa van 1.0 juist wel volledige overeenstemming tussen de beoordelaars. In de geneeskunde wordt een kappa van 0.6 tot 0.8 als goed beschouwd en een kappa van 0.8 tot 1.0

als bijna perfect. Drie deelnemende kinderneurologen (groep 1) waren leden van de DSEC groep. Drie anderen (groep 2) waren ervaren kinderneurologen: één werkzaam in een epilepsiecentrum, één in een centrum voor epilepsiechirurgie en één in een universitair kinderziekenhuis. De deelnemers kregen een uitgebreide beschrijving van de aanvallen op papier uitgereikt. Wanneer deze kinderneurologen de diagnose stelden op basis van hun persoonlijke ervaring en kennis bleek er slechts een zeer matige overeenstemming te bestaan over de aard van de aanvallen (kappa 0.19 tot 0.60, gemiddeld 0.41). Wanneer criteria werden uitgereikt waaraan een epileptische aanval moet voldoen trad een lichte verbetering op tot kappa's van 0.23 tot 0.68, gemiddeld 0.45. De kinderneurologen uit de DSEC, die gewend waren aan deze wijze van diagnosticeren, scoorden consequent hoger dan de andere drie kinderneurologen. Vervolgens werd binnen de twee groepen van drie kinderneurologen over ieder kind gediscussieerd totdat men binnen elk van de twee groepen tot één gezamenlijke diagnose kwam. De kappa tussen de diagnose van groep 1 en 2 bedroeg 0.6. Dit is beter dan de aanvankelijke onderlinge individuele overeenstemming zonder criteria voor de aanval, maar nog steeds matig. Hierbij dient beseft te worden dat in de dagelijkse praktijk geen aanvalscriteria worden gebruikt en ook geen uitgebreide bespreking plaats vindt met ervaren kinderneurologen over de diagnose. In het dagelijkse leven zal dus een vrij grote mate van verschil van mening bestaan over de aard van een eenmalige aanval. Als een diagnose betrouwbaar is te stellen zal de kappa hoog zijn. Omgekeerd betekent een hoge kappa niet automatisch een juiste diagnose. Een valkuil kan een ieder op hetzelfde verkeerde spoor zetten waardoor eensluidend een verkeerd oordeel volgt. Tot slot werden in dit onderzoek alle gegevens aan de deelnemers verstrekt zoals EEG, scan, enzovoort. Ook met deze gegevens lukte het de deelnemers slechts bij een klein aantal kinderen een specifieke syndroomdiagnose te stellen.

Hoofdstuk 4

Na het onderzoek van de onderlinge overeenstemming tussen kinderneurologen over de diagnose volgt in hoofdstuk 4 het onderzoek naar de juistheid (accuracy) van de diagnose eenmalig insult en epilepsie. Zoals in hoofdstuk 2 en 3 beschreven bestaat er geen gouden standaard voor de diagnose insult of epilepsie. De enig mogelijke wijze van controle op de diagnose is het vervolgen van patiënten. Indien uit het beloop nieuwe gegevens naar voren komen kan dit leiden tot een andere diagnose. Indien geen nieuwe aanvallen meer optreden is de kans dat de diagnose achteraf veranderd zal worden laag. Er zijn veel methoden om de mate van juistheid van de diagnose in getal uit te drukken. Dit leidt nogal eens tot verwarring.

Tabel 3a. Definities.

Vals positieve diagnose	Diagnose epilepsie gesteld terwijl kind geen epilepsie heeft: B
Vals negatieve diagnose	Diagnose geen epilepsie gesteld terwijl kind wel epilepsie heeft: C
Sensitiviteit	Het gedeelte van alle kinderen met epilepsie die al zijn herkend bij inclusie: (A)/(A+C)
Specificiteit	Het gedeelte van alle kinderen zonder epilepsie en als dusdanig herkend bij inclusie: (D)/(B+D)
Positief voorspellende waarde	Het gedeelte van alle kinderen met de diagnose epilepsie bij inclusie die achteraf ook werkelijk epilepsie hadden: (A)/(A+B)
Negatief voorspellende waarde	Het gedeelte van alle kinderen met de diagnose geen epilepsie bij inclusie die achteraf ook werkelijk geen epilepsie hadden: (D)/(C+D)

Tabel 3b. Diagnose epilepsie.

	na follow-up +	*na follow-up* -
bij inclusie +	A	B
bij inclusie -	C	D

De definities staan vermeld in tabel 3a en 3b.
Allereerst de resultaten van de kinderen met één aanval. 54% van de kinderen met de diagnose epileptische aanval kreeg na de eerste aanval nog één of meer aanvallen gedurende de daarop volgende twee jaar. Bij al deze kinderen werd de diagnose epilepsie gesteld. Er kwamen geen nieuwe gegevens naar voren waardoor de eerste aanval achteraf als niet epileptisch moest worden beschouwd. Ook bij de kinderen zonder recidief aanvallen kwamen geen nieuwe gegevens naar voren. Dus bij 0% was een vals positieve diagnose eenmalig insult (B) gesteld voor zover wij uit de gegevens uit de vervolgperiode konden opmaken. De positief voorspellende waarde van de diagnose epileptische aanval was in ons onderzoek 100% (A=170, B=0). Bij 54 kinderen (C+D) bestond onzekerheid over de aard van de aanval. Gedurende een vervolgperiode van één jaar kregen 14 kinderen nog

één of meer aanvallen. Bij vier (C) van deze 14 kinderen waren het epileptische aanvallen en moest de eerste aanval achteraf waarschijnlijk ook als epileptische aanval worden beschouwd. Bij 40 kinderen gebeurde gedurende een jaar niets meer en kwam geen nieuwe informatie beschikbaar. Bij vier (C) van de 54 (C+D) kinderen bleek dus achteraf een vals negatieve diagnose te zijn gesteld (7.4%). Bij 50 (D) van de 54 kinderen (C+D) bij wie werd gesteld dat ze geen epileptische aanval hadden doorgemaakt was dit werkelijk zo: negatief voorspellende waarde 92.6%. Bij 170 (A) van de 174 (A+C) kinderen met één epileptisch insult was dit bij inclusie herkend (sensitiviteit 97.7%). Het beloop na één aanval wordt uitvoerig besproken in hoofdstuk 6.

Bij inclusie werd bij 412 kinderen (A+B) de diagnose epilepsie gesteld (meerdere niet geprovoceerde epileptische aanvallen). Bij 367 kinderen was dit op basis van de aanvalsbeschrijving, bij 45 kinderen op basis van de aanvalsbeschrijving in combinatie met de EEG bevindingen. Gedurende twee jaar vervolg rees bij 19 (B) van deze 412 kinderen (A+B) twijfel over de diagnose epilepsie: vals positieve diagnose epilepsie 4.6%. De positief voorspellende waarde was 95.4%. Bij 124 kinderen (C+D) bestond bij inclusie onzekerheid over de aard van de aanvallen. 75 van deze kinderen kregen gedurende een vervolg van één jaar nog één of meer aanvallen. Bij 36 van deze kinderen werd een diagnose anders dan epilepsie gesteld. Bij zeven (C) werd wel alsnog de diagnose epilepsie gesteld. Bij 5.6% was dus bij inclusie een vals negatieve diagnose gesteld. De negatief voorspellende waarde was 94.4%. Uiteindelijk waren er (412-19)+7=400 kinderen met epilepsie (A+C) waarvan er 412-19 (A) waren herkend bij inclusie: sensitiviteit 393:400=98.3%. Bij 136 kinderen (B+D) werd na het vervolgen geconcludeerd dat zij geen epilepsie hadden: 124 kinderen met onduidelijke aanvallen bij inclusie, hiervan vallen er zeven af, maar komen er 19 bij die aanvankelijk de diagnose epilepsie hadden gekregen. Bij inclusie waren er hiervan 124-7=117 herkend (D): specificiteit 117:136=86%. Over de gehele groep van 760 kinderen met één of meer aanvallen was in ons onderzoek de sensitiviteit 98.1% en de specificiteit 89.8%.

In deze studie werden hoge scores bereikt wat betreft nauwkeurigheid van de diagnose op het moment van inclusie in de studie. Dit is ook zeer wenselijk bij een wetenschappelijk onderzoek. In vergelijkbare onderzoeken ontbreken deze gegevens. Een onderzoek is echter een andere situatie dan de dagelijkse praktijk. In hoofdstuk 2 wordt besproken dat in de praktijk nogal eens onjuiste diagnoses worden gesteld. In ons onderzoek werd de diagnose gesteld door ervaren kinderneurologen. Ook werd gebruik gemaakt van schriftelijk vastgelegde criteria en werden alle kinderen onderling uitvoerig besproken. Dit staat ver van de dagelijkse praktijk. Zowel bij kinderen met één als met meerdere aanvallen zonder duidelijke

diagnose zijn één of twee EEG's gemaakt. Het betrof de kinderen waar het panel van meende dat zij geen epileptische aanvallen hadden of er onvoldoende zekerheid aanwezig was om dit te concluderen. Een andere diagnose was echter niet voorhanden. Een deel van deze kinderen had wel epileptiforme stoornissen op het EEG. Drie van de acht kinderen met één onduidelijke aanval (hoofdstuk 6) en één van 27 kinderen met meerdere onduidelijke aanvallen met een epileptiform EEG bleken na één jaar follow-up toch epilepsie te hebben. De positief voorspellende waarde van het EEG bij de door ervaren kinderneurologen als onduidelijk bestempelde aanvallen was 11.4%. Hieruit blijkt opnieuw dat een goede aanvalsbeschrijving en interpretatie tot de diagnose leiden, en men bij een onduidelijk verhaal niet een diagnose op grond van EEG bevindingen kan stellen.

Hoofdstuk 5

Bij kinderen met aanvallen en verdenking op epilepsie wordt meestal een EEG gemaakt. Zoals al in hoofdstuk 2 en 4 vermeld wordt de diagnose epilepsie niet gesteld op grond van EEG afwijkingen alleen, maar voornamelijk op de aanvalsbeschrijving. Bij een groot gedeelte van de patiënten met epilepsie worden tijdens een EEG registratie ontladingen gezien met een specifieke configuratie zoals pieken en piekgolfcomplexen. Dergelijke bevindingen worden epileptiforme afwijkingen genoemd. Een aanzienlijk deel van de patiënten met epilepsie heeft dergelijke epileptiforme afwijkingen echter niet tijdens een EEG registratie. Hiervoor zijn vele oorzaken aan te geven. Een registratie duurt 30 minuten. Tijdens een EEG registratie is de kans op het doormaken van een aanval gering. Echter ook zonder aanval kunnen abnormale ontladingen optreden tijdens een EEG registratie. Bij een EEG registratie worden elektroden op de schedel aangebracht. Hiermee wordt echter alleen activiteit gemeten van de oppervlakkig gelegen hersendelen en niet van de dieper gelegen structuren. Een aanzienlijk deel van gezonde kinderen zonder epilepsie, ongeveer 3.5 tot 5%, heeft juist wel epileptiforme ontladingen tijdens een EEG registratie zonder ooit epilepsie te krijgen. Het percentage epileptiforme afwijkingen ligt nog hoger bij kinderen met neurologische aandoeningen als autisme, ADHD, mentale retardatie, ook als deze kinderen geen epilepsie hebben. Wanneer een kind aanvallen heeft die weliswaar bij epilepsie zouden kunnen passen, maar er geen volledige zekerheid bestaat kan het EEG wel de doorslag geven. De EEG bevindingen moeten passen bij de aanvalsbeschrijving. Wanneer het EEG epileptiforme afwijkingen vertoont, zullen de aard en de locatie verschillen afhankelijk van het aanvalstype en het epilepsiesyndroom. Het EEG heeft daarom in combinatie met de klinische gegevens vooral waarde bij het classificeren van

het aanvalstype en het epilepsiesyndroom. In deze samenvatting zijn als voorbeeld van epilepsiesyndromen JME en benigne rolandische epilepsie genoemd. Bij deze syndromen zijn op het EEG meestal epileptiforme afwijkingen aanwezig, die echter zeer verschillen van elkaar en kenmerkend zijn voor het betreffende syndroom.
Ook wat betreft het EEG kan de vraag worden gesteld of verschillende neurologen een EEG gelijk beoordelen. In hoofdstuk 5 staan de resultaten van ons onderzoek naar de beoordeling van het EEG door zes ervaren klinisch neurofysiologen. Steeds werd de mening van twee willekeurige neurofysiologen uit deze groep met elkaar vergeleken. Nadat zij 72 EEGs hadden beoordeeld bleek hun mening wat betreft het voorkomen van epileptiforme afwijkingen heel goed met elkaar overeen te stemmen: kappa 0.83. Het EEG kan echter ook andere minder specifieke stoornissen vertonen. Deze kunnen plaatselijk optreden (focaal) of overal in de hersenen (diffuus). Over deze stoornissen bleken de neurofysiologen het onderling niet erg eens te zijn: kappa voor diffuse stoornissen 0.53 en voor focale stoornissen 0.38. Voor een deel kan deze onenigheid worden verklaard doordat het EEG op de kinderleeftijd voortdurend verandert bij het opgroeien. Vaak is het moeilijk te beoordelen of een beeld nog wel of niet bij de leeftijd past, wat discussie geeft over het al dan niet aanwezig zijn van diffuse stoornissen. Bij kinderen komen veel variaties voor in het EEG patroon waarvan het moeilijk is te beoordelen of het EEG al dan niet normaal is. De klinisch neurofysiologen waren het in dit onderzoek vaak wel met elkaar eens dat het EEG afwijkend was, maar de één beoordeelde een stoornis als focaal en de ander dezelfde stoornis als diffuus. Nadat de klinisch neurofysiologen dit probleem onderling hadden besproken stelden zij criteria op wanneer een afwijking diffuus of focaal genoemd moest worden. In een nieuwe serie van 39 EEGs die zij beoordeelden steeg de kappa voor diffuse stoornissen naar 0.73 en voor focale stoornissen naar 0.54. Voor de praktijk zijn echter de epileptiforme stoornissen het belangrijkste. Hierover waren de klinische neurofysiologen het in hoge mate onderling eens. De betekenis van niet specifieke focale afwijkingen is in de huidige tijd afgenomen. Voorheen werd dit gebruikt om onderliggende structurele afwijkingen in de hersenen op te sporen. Tegenwoordig kan dit met kwalitatief zeer hoogwaardige afbeeldingapparatuur (MRI scan).
Ook over dit onderzoek zijn een aantal eerdere opmerkingen van toepassing. Onze klinisch neurofysiologen waren zeer goed in staat onderling reproduceerbaar epileptiforme functiestoornissen te beoordelen. Het betreft echter wederom zeer gespecialiseerde medici met onderzoekservaring. Een EEG op de kinderleeftijd is moeilijk te beoordelen. Het EEG verandert voortdurend met de leeftijd. Kinderen bewegen vaak tijdens het onderzoek wat storing (artefacten) op het EEG geeft. Ook andere factoren kunnen storing veroorzaken. Artefacten kunnen veel

gelijkenis vertonen met epileptiforme stoornissen. In de dagelijkse praktijk heeft niet ieder ziekenhuis klinisch neurofysiologen, of kan de ervaring met kinderen beperkt zijn. Hierdoor kunnen normale verschijnselen of artefacten voor epileptiforme stoornissen worden aangezien. In hoofdstuk 2 is besproken dat EEG bevindingen een grote bron van misverstand kunnen zijn en tot een verkeerde conclusie over het al dan niet bestaan van epilepsie kunnen leiden. Zolang een kind geen aanvallen heeft, heeft het kind geen epilepsie, ook niet als er epileptiforme afwijkingen op het EEG zijn. Bij bijvoorbeeld hoofdpijn en gedragsproblemen zal een EEG alleen maar verwarring veroorzaken. Een EEG dient daarom bij kinderen te worden gemaakt als er op grond van de aanvalsbeschrijving verdenking is op epileptische aanvallen. Het EEG dient te worden beoordeeld door een klinisch neurofysioloog met ervaring met kinder-EEGs. Degene die het EEG aanvraagt dient op de hoogte te zijn van alle valkuilen en het EEG zonodig te bespreken met de klinisch neurofysioloog. Indien het EEG op de juiste indicatie wordt aangevraagd, door een deskundige wordt beoordeeld, en overleg plaats vindt tussen aanvrager en beoordelaar is het EEG een zeer waardevol gegeven bij de diagnostiek en classificatie van epilepsie. Indien dit niet gebeurt, kan een EEG zeer nadelige gevolgen hebben voor de patiënt.

Hoofdstuk 6

In hoofdstuk 6 wordt het onderzoek bij kinderen met een eenmalige (niet acuut symptomatische) epileptische aanval beschreven. De onzekerheid van de diagnose is in hoofdstuk 2 t/m 4 besproken. Andere vragen zijn: hoe groot is de kans op herhaling, ofwel hoe groot is de kans op epilepsie? Welke kinderen krijgen meer aanvallen en hoe vergaat het deze kinderen vervolgens? Er waren voor ons onderzoek eerdere onderzoeken gedaan. Deels betrof het onderzoeken van patiënten van alle leeftijden zonder onderscheid te maken tussen kinderen en volwassenen. Er waren echter ook diverse onderzoeken specifiek bij kinderen uitgevoerd. In deze onderzoeken was het risico op herhaling van de aanvallen zeer uiteenlopend. Hiervoor zijn meerdere oorzaken aan te wijzen. In geen enkel onderzoek werd vermeld hoe de diagnose werd gesteld en of deze achteraf moest worden bijgesteld. In alle onderzoeken kreeg een deel, en vaak zelfs een groot deel van de kinderen direct AEDs voorgeschreven na één aanval. Aannemelijk is dat dit de herhalingskans van aanvallen verlaagt. Het interval tussen aanval en inclusie in het onderzoek is vaak niet genoemd. Duidelijk is dat recidiefaanvallen vaak heel snel na de eerste aanval volgen. Als er een lange wachttijd is voordat kinderen worden gezien in een ziekenhuis zullen er minder kinderen met een eenmalige aanval overblijven. Velen

hebben in de wachttijd al een recidief gehad. De kinderen die na de wachttijd nog geen nieuwe aanval hebben doorgemaakt hebben een lager risico op herhaling omdat dit risico met het verstrijken van de tijd steeds lager wordt.
In ons onderzoek werden kinderen relatief snel gezien en geïncludeerd (49% <24 uur en 71% <zeven dagen); de diagnose werd gesteld op grond van de aanvalsbeschrijving met behulp van criteria; het EEG werd bij de diagnose eenmalig insult buiten beschouwing gelaten. Wel werd bij alle kinderen een EEG gemaakt en indien niet afwijkend een tweede EEG na partiële slaapdeprivatie (een korte nachtrust). Verreweg de meeste kinderen hadden een tonisch-clonisch insult ("grote aanval") doorgemaakt al dan niet met een partiëel begin. Geen enkel kind kreeg AEDs na de eerste aanval. In vergelijking met andere onderzoeken kreeg een relatief groot deel van de kinderen, 54%, meer aanvallen binnen twee jaar. Naar alle waarschijnlijkheid is dit toe te schrijven aan onze nauwkeurige methodiek, het niet direct behandelen en de snelle inclusie. Ook bij ons was de kans op nieuwe aanvallen het grootste in de eerste zes maanden (figuur 2 in hoofdstuk 6). De risicofactoren voor herhaling waren epileptiforme stoornissen op het EEG en/of het aanwezig zijn van neurologische afwijkingen of een verstandelijke handicap (dus een laat symptomatische aanval). Bij afwezigheid van deze factoren was de herhalingskans 40% en bij aanwezigheid van deze factoren 71-74% (figuur 3 en 4 in hoofdstuk 6). De 85 kinderen die een recidief kregen zijn vervolgens 24-72 maanden vervolgd (gemiddeld 42 maanden). Op het einde van de follow-up waren 50 van deze kinderen minstens 12 maanden aanvalsvrij, en hadden er 22 nog aanvallen in de laatste zes maanden. Gerekend voor alle kinderen geïncludeerd met één epileptische aanval was dus op het einde van de follow-up 78% minstens 12 maanden aanvalsvrij, terwijl 14% nog aanvallen had de laatste zes maanden. In deze laatste groep waren echter ook kinderen die met een lage frequentie tonisch-clonische insulten of rolandische aanvallen hadden, waarvan er één of een enkele in het laatste half jaar van de follow-up plaats vond. De kans dat een kind zich presenteert met één epileptische aanval en daarna een langdurige vervelende epilepsie ontwikkelt is laag. Bij ernstige epilepsiesyndromen op de kinderleeftijd komen vaak kleinere aanvallen voor in een hoge frequentie. Die kinderen zullen niet na één aanval worden gezien, enerzijds omdat de eerste aanval vaak niet als iets abnormaals wordt herkend, anderzijds zullen door de hoge aanvalsfrequentie al vele nieuwe aanvallen zijn gevolgd op het moment dat een arts wordt geraadpleegd.
Wat zijn de conclusies voor de praktijk? De eerste vraag was: hoe zeker is de diagnose epileptische aanval? Uit het voorgaande is duidelijk dat er vaak een forse mate van onzekerheid zal bestaan. De volgende vraag betrof de herhalingskans als een epileptische aanval erg waarschijnlijk lijkt? Deze loopt uiteen van 40% tot

74% De door ons gevonden risicofactoren voor het ontstaan van epilepsie stemmen overeen met die van enkele andere grote onderzoeken: de resultaten van het EEG en de oorzaak van de aanval (laat symptomatisch). Niettemin krijgt 26-29% van de kinderen met deze risicofactoren geen epilepsie. De laatste vraag is: wat is de winst van het direct na één epileptische aanval voorschrijven van AEDs aan kinderen? In ons onderzoek is de kans op een moeilijk behandelbare chronische epilepsie vrij klein voor kinderen die zich presenteren met één aanval. Vóór onze studie is in Canada een onderzoek gedaan bij een kleine groep van 31 kinderen. De ene helft kreeg een AED, de andere helft niet. Van de behandelde kinderen kregen er minder recidiefaanvallen dan van de onbehandelde kinderen. Een deel van deze kinderen kreeg echter vervelende bijwerkingen van de medicatie. Uiteindelijk was het aantal kinderen dat klachtenvrij was even groot in beide groepen: de winst door minder aanvallen was volledig verloren gegaan door het optreden van bijwerkingen bij de behandelde kinderen. Vijftien jaar later is opnieuw gekeken hoe het met deze kinderen ging. Er was geen verschil in het aantal doorgemaakte epileptische aanvallen tussen de direct behandelde kinderen en de controle groep. Van de direct behandelde kinderen was na 15 jaar 80% minstens twee jaar aanvalsvrij en van de controlegroep 88%. Hierna zijn geen nieuwe (grotere) onderzoeken gedaan naar het effect van behandeling specifiek bij kinderen. Wel zijn twee onderzoeken gedaan waaraan zowel kinderen als volwassenen meededen zonder dat bij de analyse onderscheid werd gemaakt. In een Italiaans onderzoek betrof het patiënten met uitsluitend één aanval, in een Engels onderzoek patiënten met één of enkele aanvallen. In beide onderzoeken kwam naar voren dat behandelde patiënten in de eerste periode minder aanvallen doormaakten. Na langere tijd verdween dit verschil en was het aantal aanvalsvrije patiënten precies even groot geworden ongeacht of er wel of niet direct na de eerste aanval met AEDs werd gestart. Naar de nadelige effecten van medicatie is niet gekeken in het Italiaanse onderzoek. In het Engelse onderzoek was er geen verschil in "quality of life" of complicaties tussen beide groepen. Na vijf jaar gebruikten echter wel veel meer patiënten (60%) AEDs in de groep die direct werd behandeld in vergelijking met de groep die niet of later werd behandeld (41%). Een vierde vraag, deels al beantwoord, is of er gevaren zijn verbonden aan het niet direct behandelen. De kans op een onbehandelbare epilepsie neemt niet toe. In ons onderzoek zijn geen kinderen overleden door een aanval, ook niet in de groep kinderen die zich presenteerde met meerdere aanvallen. Ook in een groot Amerikaans onderzoek werd na een eerste aanval geen sterfte gemeld door nieuwe aanvallen. Wel is de sterfte onder kinderen met epilepsie hoger dan onder kinderen zonder epilepsie. Dit is echter een gevolg van de ziekte die de epilepsie veroorzaakt, bijvoorbeeld

een progressieve onbehandelbare stofwisselingsziekte. Al met al zijn er geen harde argumenten om direct na een eerste aanval met medicatie te starten. In geval van twijfel zal de tijd bij een deel van de kinderen de aard van de aanvallen alsnog duidelijk maken, of de aanvallen verdwijnen spontaan. In de groep kinderen die wel nieuwe aanvallen krijgt bevinden zich ook kinderen met zogenaamde benigne (goedaardige) epilepsie. Deze kinderen hebben meestal maar weinig aanvallen, vaak alleen in de slaap, en na enige tijd verdwijnen de aanvallen spontaan. Op grond van ons onderzoek en enkele andere onderzoeken hebben the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society richtlijnen uitgebracht over eventueel onderzoek (2000) en behandeling (2003) bij een kind met één epileptische aanval: "een EEG wordt aanbevolen, maar ander onderzoek wordt alleen nodig geacht als daar aanleiding toe is op grond van specifieke omstandigheden. Behandeling is niet nodig om epilepsie te voorkomen en verbetert niet de prognose. Behandeling kan worden overwogen als de voordelen van het verlagen van de kans op nieuwe aanvallen opwegen tegen het risico van de bijwerkingen en de psychosociale effecten."

Hoofdstuk 7

In hoofdstuk 7 staat het beloop beschreven van kinderen met epilepsie die eenmaal of vaker een status epilepticus (SE) doormaakten. Toen de DSEC startte waren hierover geen gegevens bekend. Zeer langdurige aanvallen noodzaken vaak tot opname op een intensive care afdeling. Door de lange duur van de aanval en door de behandeling kunnen allerlei complicaties optreden. Met SE worden meestal epileptische aanvallen aangeduid die 30 minuten of langer duren. Deze tijdsduur in de definitie was gebaseerd op gegevens uit proefdierenonderzoek. Uit dergelijk onderzoek kwamen aanwijzingen dat na een dergelijke duur schade kon optreden aan de hersenen. De afgelopen jaren is over deze tijdslimiet om meerdere redenen discussie ontstaan. Het is gebleken dat als een aanval eenmaal vijf tot 10 minuten duurt de kans dat deze aanval stopt zonder medisch ingrijpen sterk afneemt. Tevens is uit diverse onderzoeken gebleken dat naarmate sneller wordt ingegrepen de kans groter is dat de aanval makkelijker met noodmedicatie kan worden gestopt. Anderzijds lijkt ondertussen het ontstaan van schade aan de hersenen door een aanval van 30 minuten veel minder waarschijnlijk. Ook blijkt dat de aanvalsfrequentie en de aanvalsduur onafhankelijke variabelen zijn. De meeste patiënten hebben alleen korte aanvallen, een minderheid heeft lange aanvallen. Omdat de meeste aanvallen spontaan stoppen binnen vijf minuten, en de kans dat dit alsnog gebeurt na vijf minuten sterk afneemt is het huidige advies na vijf

minuten noodmedicatie toe te dienen. Indien dit advies wordt uitgevoerd treden aanzienlijk minder complicaties op. Gezien deze gegevens pleit een aantal onderzoekers ervoor de tijdsduur in de definitie van SE te wijzigen in vijf of tien minuten. Toen de DSEC startte was de enige definitie van SE die van 30 minuten. Deze definitie is ook gebruikt in twee andere onderzoeken die recent zijn uitgevoerd.
Bijna 10% van de kinderen met epilepsie in de DSEC maakte een SE door. Voor de meeste kinderen (68%; 32 van de 47) was het hun eerste epilepsieaanval. 41 van deze 47 kinderen (87%) had al een SE op het moment dat ze werden verwezen naar het ziekenhuis. Slechts zes kinderen kregen voor het eerst een SE nadat ze al bekend waren met epilepsie. In ons onderzoek werden geen kinderen geïncludeerd met alleen acuut symptomatische aanvallen. Koortsstuipen zijn bij jonge kinderen de belangrijkste oorzaak van SE. Ondertussen zijn ook resultaten gepubliceerd van een Amerikaans en een Fins onderzoek naar het beloop van epilepsie bij kinderen die eenmaal of vaker een SE doormaakten. In deze twee onderzoeken zijn kinderen met een SE door koorts wel geïncludeerd. Als hiervoor wordt gecorrigeerd komt SE in onze groep ongeveer evenveel voor als in het Amerikaanse onderzoek. In de Finse studie was SE iets frequenter. In die studie werden echter andere onderzoeksmethoden gebruikt en waren de kinderen al in de zestiger jaren geincludeerd. Dit maakt vergelijking moeilijker. In alle onderzoeken komt een SE het vaakste voor aan het begin van de aandoening. Als in onze studie een kind eenmaal een SE had doorgemaakt was de kans op herhaling van een SE ruim 30%. De Amerikanen vonden eenzelfde herhalingskans. Van de kinderen zonder SE bij inclusie maakte in ons onderzoek slechts ruim 1% alsnog een SE door. Opvallend is dat in ons en in het Finse onderzoek kinderen met een SE voorheen vaak koortsstuipen hadden doorgemaakt, maar in het Amerikaanse onderzoek niet. In alle onderzoeken bestaat een trend dat kinderen die een SE hebben doorgemaakt een iets lagere kans hebben op den duur aanvalsvrij te worden. Significant (zeker) is dit verschil echter niet. Bovendien blijkt dat vooral kinderen met laat symptomatische epilepsie en cryptogene epilepsie een SE doormaken. Ook zonder SE is de prognose bij laat symptomatische en cryptogene epilepsie minder goed. Een uitzondering in ons en het Amerikaanse onderzoek waren de kinderen die na inclusie SE doormaakten. Echter ook kinderen met korte aanvallen die aanvallen bleven houden deden het slechter. Het gegeven dat aanvallen door blijven gaan betekent per definitie dat de epilepsie niet goed behandelbaar is. De sterfte was in geen van de drie onderzoeken hoger bij kinderen met SE. De oorzaak van de epilepsie lijkt derhalve belangrijker voor de prognose dan de aanvalsduur. Hierbij dient aangetekend te worden dat kinderen met een SE in de westerse wereld redelijk snel en adequaat kunnen worden behandeld. Uit andere onderzoeken is

bekend dat er ook kinderen en volwassenen zijn met een SE bij wie het aanzienlijk slechter kan aflopen. Er kan een aanzienlijke sterfte optreden en patiënten kunnen ernstige schade overhouden aan de hersenen. Dit zijn echter geen patiënten met epilepsie, maar patiënten met een acuut symptomatische SE door bijvoorbeeld ernstig zuurstoftekort na een hartstilstand of hersenletsel door een ongeval. Ook bij deze patiënten blijkt niet de SE zelf verantwoordelijk voor de prognose, maar de ernst van de ziekte die de SE tot gevolg had. In de DSEC onderzochten wij SE bij kinderen met epilepsie en geen acuut symptomatische aanvallen.
Aangezien er wel een hoge kans is op herhaling bij kinderen met een doorgemaakte SE dienen ouders en/of verzorgers goed geïnstrueerd te zijn hoe te handelen bij een eventueel recidief en noodmedicatie te worden voorgeschreven. Deze instructies dienen ook schriftelijk te worden meegegeven. Noodmedicatie kan ook buiten het ziekenhuis rectaal, via het wangslijmvlies of via het neusslijmvlies worden toegediend door ouders of verzorgers. Als een aanval 10 minuten na toediening niet stopt moet een ambulance worden gebeld.
Al met al verschilt de prognose dus niet veel voor kinderen met lange aanvallen (SE) van kinderen met korte aanvallen. De oorzaak van de epilepsie is een belangrijkere factor voor de prognose. De afwegingen voor het al dan niet voorschrijven van AEDs kunnen dus hetzelfde zijn voor kinderen met of zonder SE. Lange aanvallen zullen ouders echter nog meer angst inboezemen dan korte aanvallen. Hierdoor zullen ouders en artsen waarschijnlijk eerder geneigd zijn tot het gebruik van AEDs bij kinderen die een SE doormaakten.

Slot

Samengevat bestaat er op de kinderleeftijd een groot scala aan paroxysmale (met aanvalsgewijs optredende symptomen) aandoeningen. De diagnose wordt voornamelijk gesteld op de beschrijving van deze aanvallen door getuigen. Vooral in het begin van de aandoening kan een diagnose moeilijk te stellen zijn en bestaat er vaak onzekerheid over de aard van de aanvallen. Er zijn momenteel geen aanwijzingen dat in een vroeg stadium behandelen van epilepsie de prognose verbetert. De diagnose dient daarom zorgvuldig gesteld te worden, AEDs dienen alleen te worden voor geschreven aan die kinderen waar de diagnose zeker is, en nadat voor dit kind alle voor- en nadelen van behandeling goed zijn overwogen, en dit alles in overleg met ouders en kind.

Abbreviations

AED(s)	anti-epileptic drug(s)
CI	confidence interval
CVA	cerebrovasculair accident
DSEC	Dutch Study of Epilepsy in Childhood
EEG(s)	electroencephalogram(s)
ILAE	International League Against Epilepsy
JME	Juveniele myoclonus epilepsie
LR	longest remission ever
TR	terminal remission
TR5	terminal remission at five years of follow-up
SE	status epilepticus
se	standard error
ZHKO	Zuid-Hollands Kinderepilepsie Onderzoek

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Curiculum vitae

Hans Stroink is geboren op 20 december 1953 in Zwijndecht. Hij kon nog de ouderwetse middelbare schoolopleiding HBS-B volgen aan de Openbare Scholengemeenschap Prof. Casimir in Vlaardingen. Van 1971 tot 1978 volgde hij de studie geneeskunde aan de Medische Faculteit Rotterdam (vanaf 1973 Erasmus Universiteit Rotterdam, ontstaan uit de fusie met de Nederlandse Economische Hogeschool).
De opleiding tot neuroloog vond plaats van 1978 tot 1983 in het Academisch Ziekenhuis Rotterdam-Dijkzigt/Sophia Kinderziekenhuis. Gedurende deze opleiding volgde hij één extra jaar opleiding kinderneurologie.
Vervolgens was hij van 1983 tot 1999 als kinderneuroloog staflid van de afdeling neurologie Academisch Ziekenhuis Rotterdam Dijkzigt/Sophia Kinderziekenhuis (sinds 2001 Erasmus MC).
Sinds 1999 is hij werkzaam als kinderneuroloog in Tilburg, aanvankelijk in het St. Elisabeth Ziekenhuis en Tweesteden Ziekenhuis, sinds juli 2007 in het Tweesteden Ziekenhuis. Per 1 augustus 2008 treedt hij als kinderneuroloog in dienst van het Canisius-Wilhelmina Ziekenhuis in Nijmegen.
Hans Stroink is gehuwd en heeft twee zoons.

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