# Course and Long-Term Outcome of Childhood-Onset Epilepsy
# Dutch study of epilepsy in childhood

# Beloop en lange termijn prognose van kinderen met epilepsie
# Het Zuid-Hollands kinderepilepsie onderzoek

**Ada T. Geerts**

Cover illustratie: Net als een kameleon heeft epilepsie veel uitingsvormen.

Cover ontwerp: Simone Stegeman

Uitgever: GVO drukkers & vormgevers B.V. | Ponsen & Looijen



ISBN/EAN: 978-90-6464-583-9

Course and long-term outcome of childhood-onset epilepsy

(Dutch study of epilepsy in childhood)

# Course and long-term outcome of childhood-onset epilepsy
# Dutch study of epilepsy in childhood

# Beloop en lange termijn prognose van kinderen met epilepsie
# Zuid-Hollands kinderepilepsie onderzoek

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

19 oktober 2012 om 11.30 uur

Adamina Trijntje Geerts

Geboren te Hoogeveen

## Promotiecommissie

**Promotor:**

Prof. dr. W.F.M. Arts

**Overige leden:**

Prof. dr. P. Sillevis Smitt

Prof. dr. H.A. Moll

Prof. dr . P. Boon

**Copromotor:**

Dr. C.A. van Donselaar

**Acknowledgements**

This study was financially supported by the Dutch National Epilepsy Fund, Houten, the Netherlands (A72, A85, A86, and grant number 05-06) and by the JANIVO fund and Stichting Epilepsia.
The publication of this thesis was financially supported by Epilepsie Vereniging Nederland, and by Erasmus University Rotterdam.

Voor mijn lieve Peter, Charlotte, Roderik en Sebastiaan
Voor mijn lieve vader en moeder die er niet meer zijn

# Table of contents

# Chapter 1 Introduction

The topic of this thesis is epilepsy in childhood. For those who are not familiar with this disorder a short overview will be presented of epilepsy and its possible causes. In addition, some insight of how many patients suffer from epilepsy and which persons are at higher risk for developing epilepsy will be given. One should bear in mind that epilepsy is not a single condition, but a diverse family of disorders, having in common an abnormally increased predisposition to seizures [1]. This diversity will be highlighted, as well as the consequences of having epilepsy. Next, some topics of international epilepsy research are presented and finally the motives for the Dutch study of epilepsy in childhood will be explained, followed by an overview of the study.

Epilepsy is a well-known neurological disorder that is characterized by epileptic seizures. According to the latest definition, a person has to have at least one epileptic seizure in association with an enduring disturbance of the brain capable of giving rise to other seizures [1]. During a seizure an electrical imbalance in the brain prohibits normal functioning, and mostly causes absent or lowered consciousness and involuntary movements. Some patients may experience strange sensations, like seeing or hearing things that are not there. The majority of seizures last for about 30 seconds to 20 minutes, and most seizures stop spontaneously. Sometimes a seizure or successive seizures without the return of consciousness in-between can last for at least half an hour, in which case we speak of a status epilepticus. Any major seizure lasting more than five minutes is a threatening situation and needs to be stopped to prevent damage to the brain, heart or other organs.

Unlike most other illnesses and disorders, there are many causes for epilepsy. Acquired brain injuries which can be traumatic (accidents, physical trauma) or non-traumatic (tumor, stroke, infection, hypoxia) are one of the main causes. Further, one can have a genetic predisposition or a hereditary genetic abnormality causing specific types of epilepsy. Abnormal brain chemistry on the level of neurotransmitter and ion channel functioning, as well as congenital structural abnormalities in the brain can cause seizures, but also external factors - like alcohol, drugs, or metabolic disturbances, e.g. hypoglycemia or hypocalcaemia. In the latter case, we don't speak of epilepsy, as mostly there is no enduring disturbance of the brain once these external factors are eliminated.

We can categorize the causes of epilepsy (in other words: 'etiology') into idiopathic, cryptogenic and remote symptomatic [2]. An idiopathic etiology means that there is no underlying cause other than a possible hereditary predisposition. The term cryptogenic is used when the cause is presumed

to be symptomatic but is unknown. A remote symptomatic etiology is the consequence of a known or suspected disorder of the central nervous system. This classification was proposed in the starting years of the Dutch study of Epilepsy in Childhood. In 2011, new terminology and concepts to classify etiology and epilepsies were recommended and are still under discussion [3].

Epilepsy can develop at all ages. In the Netherlands the incidence of epilepsy in 2007 was 0.52 per 1000 males (95% CI: 0.37-0.73) and 0.46 per 1000 females (95% CI: 0.32-0.67). The point prevalence on January 1st in that year was 7.0 per 1000 males (95% CI: 5.32-9.22) and 6.82 per 1000 females (95% CI: 5.17-9.01) [4]. These data were based on general practitioner registrations. **Figure 1.1** and **Figure 1.2** present the incidence and prevalence of epilepsy per age-group and gender. These show that the incidence and prevalence are increased in childhood and in the elderly. In childhood, this mostly results from genetic, neurological or developmental defects and hypoxemia during pregnancy or delivery causing early onset of seizures. In elderly people epilepsy mostly results from cerebrovascular disease, primary neurodegenerative disorders, brain tumors and traumatic head injury [5].

**Figure 1.1: Incidence of epilepsy in 2007**

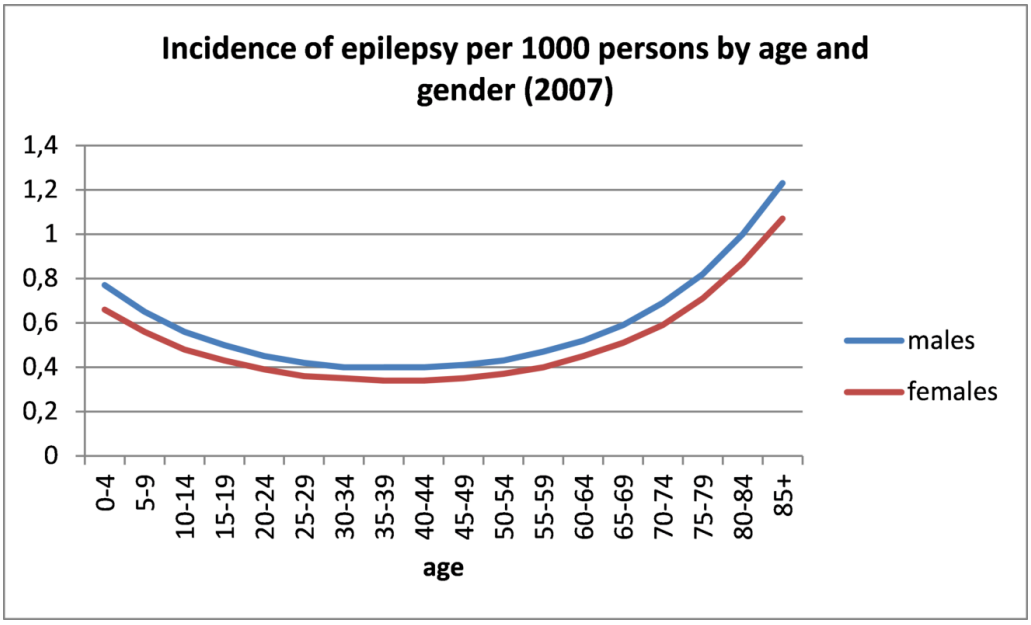
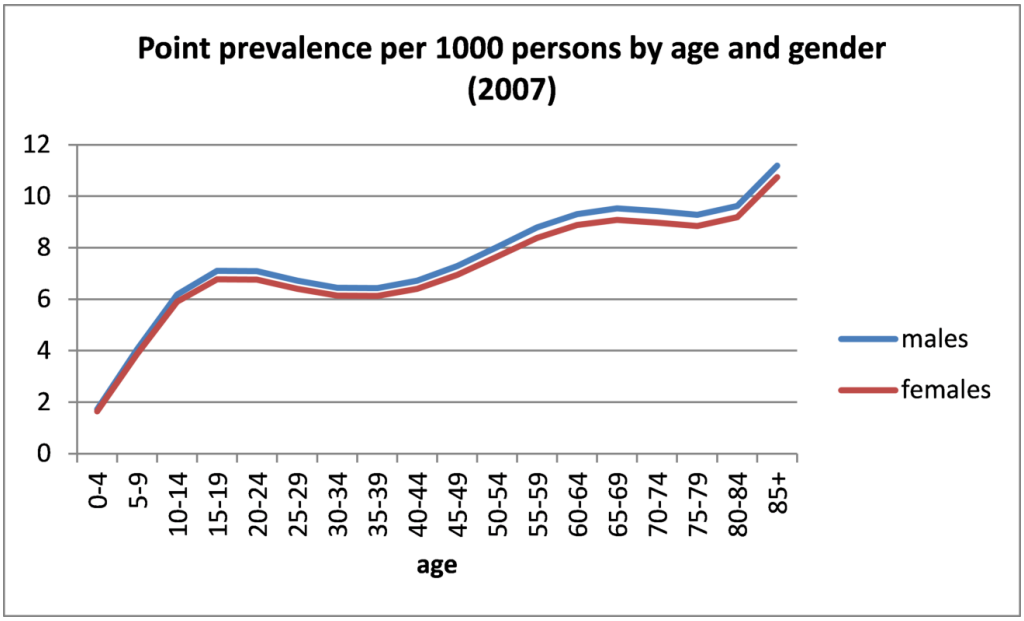


**Figure 1.2: Prevalence of epilepsy in 2007**




During childhood and adolescence, the brain is still developing and this makes childhood-onset epilepsy different from adult-onset epilepsy. In general, there are many types of epilepsy and syndromes with a diverse manifestation and course during time. Some types of epilepsy start during childhood such as benign Rolandic epilepsy or childhood absence epilepsy and stop before patients have become adults. Many other types of epilepsy start during childhood too, but most of them continue in adulthood. Juvenile myoclonic epilepsy for example starts between the ages 8 to 20 years. Patients with this type of epilepsy have a lifelong risk of seizures but seizures are mostly well-controlled by antiepileptic drugs and by avoidance of precipitants such as lack of sleep or alcohol. More severe types of epilepsy are e.g. West, Dravet's or Ohtahara syndrome, which all begin during infancy. In case of West syndrome the prognosis depends on the underlying cause which is in many cases tuberous sclerosis. Most of these patients will have mental retardation and continuing seizures and for some this syndrome will evolve into Lennox-Gastaut syndrome with multiple seizure types (mostly drop attacks) which not always respond to treatment. Dravet's syndrome starts in children with a normal development. At onset most seizures are associated with fever. Later, most seizures are prolonged with a risk of status epilepticus, seizure frequency increases and more seizure types occur. Patients do not respond well to treatment and suffer from additional complications such as autism spectrum disorders, orthopedic or movement disorders, and

infections. The prognosis of patients with the syndrome of Ohtahara is very poor, with half of the infants dying before the age of two. Those surviving are severely mentally handicapped.

Treatment of epilepsy is primarily focused on the prevention of seizures or in case this is not possible on the reduction of seizure frequency and severity. Several epilepsy types require specific treatment strategies. This calls for an accurate diagnosis and classification (mostly based on the description of the seizures and results of diagnostic investigations, such as EEG, CT-scan, or MRI) followed by an appropriate treatment.

Beside the short-term physical consequences of having a seizure such as confusion, headache, or myalgia, patients with epilepsy are confronted with long-term consequences they have to deal with. The facts that they are suddenly facing a neurological disorder, have unpredictable seizures that influence their daily life, and need to take medication with a high chance of side-effects, may become very frustrating. In addition, the fear for new seizures and dying may be overwhelming. Beside this, epilepsy not only reduces the opportunity of getting a driver's license, it also may have great impact on social well-being, the chance to make friends, find a partner, have kids, but also on cognitive development, education and employment. All these aspects influence a patient's well-being, self-esteem and quality of life and should be recognized and dealt with by the treating physician and other caregivers involved, such as the epilepsy nurse.

The wide scale of epilepsy types and syndromes during the early years of life, together with all aspects of epilepsy mentioned above, make childhood-onset epilepsy an inexhaustible source for scientific research. Worldwide, there have been several cohort studies focusing on aspects, such as long-term medical prognosis of epilepsy, the risk of status epilepticus, the development of intractability, possible increased mortality, educational or social prognosis, and quality of life (**Table 1.1**). Another area of research is that focusing on alternative or additional treatment strategies for patients with epilepsy not responding to antiepileptic drugs (epilepsy surgery, ketogenic diet, and nervus vagus stimulation).

Despite all research efforts, a lot of questions remained unanswered or the results found needed further confirmation. Worldwide in the years 80, for example, there was dispute on the treatment strategy of children with only one seizure, or when to safely stop treatment in children after remission. Some even reported that delaying AED-treatment might lead to an accelerating seizure pattern of epilepsy with a higher risk of becoming intractable [6].

**Table 1.1: Cohorts of subjects with childhood-onset epilepsy arranged by length of follow-up**

| | Original size of the cohort | | Age at inclusion | Years of inclusion | Mean FU in years | references |
|---|---|---|---|---|---|---|
| Sillanpaa et al., Finland, Turku | 150 incident cases<br>95 prevalent cases | Partly retrospective population based | 15 years or less | 1961 – 1964 | 37.0 (SD 7.1, median 40.0, range11-42) for 144 of the 150 incident cases.<br>Etiology of 150 incident cases:<br>31% idiopathic<br>25% cryptogenic<br>44% remote symptomatic | [7-23] |
| Chin et al., United Kingdom, London | 101 | Prospective population based. Children with epilepsy which were part of a birth cohort representing 98% of all births in Britain during one week in 1958 (National Child Development Study). Questionnaires at age 7, 11, 16, 23 and 33 years of age. | Onset of epilepsy at 16 years or less | 1958 | 33 years since birth<br>Etiology of 101 cases:<br>50% idiopathic<br>50% symptomatic (including cryptogenic) | [24-26] |
| Kokkonen et al., Finland, Oulu | 81 | Non-institutionalized patients with childhood-onset epilepsy born between 1964 and 1967 | | 1964 - 1967 | Mean age 22.3 years<br>Etiology of 81 cases:<br>46% idiopathic<br>33% cryptogenic<br>19% symptomatic | [27, 28] |
| Wakamoto et al., Japan, Uwajima | 155 | Partly retrospective hospital based: 92% of catchment area | 15 years or less | 1961 - 1992 | 18.9 (± 5.3, range 6-37.5) for 148 remaining subjects.<br>Etiology of 155 cases:<br>40% idiopathic<br>13.5% cryptogenic<br>46.5% remote symptomatic | [29] |
| Casetta et al., Italy, Copparo | 111 incident cases | Only incident cases with idiopathic and cryptogenic epilepsy from an epidemiological study on incidence and prevalence of epilepsy. Community-based, representative of population of interest. | 0 - 19 years | 1964-1978 | 18.8 years (± 1 SD, range 7-24)<br>No frequencies of idiopathic or cryptogenic epilepsy are presented. | [30-33] |
| Arts et al., The Netherlands, Western Region | 466 incident cases | Prospective hospital based: 75% of catchment area | 1 month to 16 years | 1988 - 1992 | 14.8 (11.6-17.5) for 413 remaining subjects.<br>Etiology of 413 cases:<br>51% idiopathic<br>21% cryptogenic<br>28% remote symptomatic | [34-51] |
| Shinnar et | 407 with | Prospective hospital based | 1 month to | 1983 – 1992 | 14.2 after 1st seizure | [52, 53] |

| | Original size of the cohort | | Age at inclusion | Years of inclusion | Mean FU in years | referen ces |
|---|---|---|---|---|---|---|
| al., USA, Bronx NY | first seizure, 182 of them with 2 or more seizures | The predominantly inner-city minority population was representative of the mixture of patients seen at the institutions. It consisted of (38%) Hispanic children, (28%) white children, (29%) black children, and (4%) children of other ethnic origins. | 19 years | after 1st seizure. The mean age at the time of first seizure was 6.8 years. | Etiology of 182 case followed for 8.2 years after 2nd seizure:<br>25% idiopathic<br>49% cryptogenic<br>26% remote symptomatic | |
| Camfield et al., Canada, Halifax | 686 | Partly retrospective population based on two cohorts: one excluding myoclonic, akinetic, atonic and intfantile spasms, the other with only absence seizures. | 1 month to 16 years | 1977 - 1985 | 13 (median 13.9, range 0-22.5) for 660 remaining subjects.<br>Etiology of 602 cases:<br>31% idiopathic<br>35% cryptogenic<br>34% remote symptomatic | [54-65] |
| Brorson and Wranne, Sweden, Uppsala | 68 incident cases<br>126 prevalent cases | Partly retrospective population based | 10 - 19 | 1962 – 1964<br>Before 1962 | FU study in 1976 – 1977: after 12 years<br>Etiology of prevalent cases:<br>54.8% neurodeficit (MR +/- abn. Neurology)<br>Etiology of incident cases:<br>25% neurodeficit | [66] |
| Berg et al., USA, Connecticut | 613 | Prospective hospital based with probably high level of representativeness | 1 month to 16 years | 1993 - 1997 | Median 10.5 (8% < 5 years)<br>Etiology of 613 cases:<br>30% idiopathic<br>52% cryptogenic<br>18% remote symptomatic | [67-83] |
| Kwong et al., China, Hong Kong | 309 prevalent cases with active epilepsy | Hospital based: nearly population based | 15 years or less | < 1997 | 4.9 for 255 subjects.<br>Etiology of 309 cases:<br>42% idiopathic<br>16.8% cryptogenic<br>40.8% remote symptomatic | [84, 85] |
| Oskoui et al., Canada, Montreal | 196 | Retrospective hospital based | 2 – 17 years | 1991 - 2000 | 4.6 (±2.5, range 2.0-13.6)<br>Etiology of 196 cases:<br>50% idiopathic<br>32% cryptogenic<br>18% remote symptomatic | [86, 87] |
| Wirrell et al.,USA,. Rochester | 359 incident cases | Cases were retrospectively ascertained by review of diagnostic index of the Rochester Epidemiology Project | 1 month – 17 years | 1980-2004 | 111 cryptogenic focal epilepsy with FU> 1 year (Median 13.1)<br>95 symptomatic focal epilepsy with FU> 1 year (Median 11.2) | [88-90] |

In treatment decisions there has to be a balance between the intended prevention of seizures with anti-epileptic drugs and the risk of possibly severe side effects of these drugs. Exposing children to unnecessary treatment has to be avoided. On the other hand, stopping medication too early may increase the risk for recurrent seizures. It was evident at that time that more research was needed to solve these treatment dilemmas in children with epilepsy.

The central theme in these dilemmas was predictability. Would it be possible to predict early in the course of the disease which children will have a favorable prognosis, permitting a more relaxed policy regarding starting and stopping of medication, or would it be possible to predict which children have a poor prognosis, probably requiring more aggressive treatment, including for example early referral for epilepsy surgery. In addition, there was a need for information about factors determining the favorable or poor prognosis of childhood-onset epilepsy, either alone or in combination.

To answer these questions a large cohort study was needed to follow children with newly diagnosed epilepsy. Worldwide there were not many large cohort studies prospectively following children since their diagnosis of epilepsy. That's why the Dutch Study of Epilepsy in Childhood was started in which children who attended hospital with new-onset epilepsy were consecutively recruited between 1988 and 1992. In contrast to research in specialized Dutch epilepsy centers (mostly treating the more severe cases), this prospective cohort study was the first large study conducted in regular and academic hospitals in the Netherlands, and had the advantage of observing the course, outcome and treatment effects of ‘more average’ epilepsy in children in detail almost from the time of onset. The aim of the study and methods are further described in the next paragraph.

**The Dutch Study of Epilepsy in Childhood:**

Neurologists and pediatric neurologists of two university hospitals, one general and one children’s hospital in the western region of the Netherlands agreed to prospectively study children with at least one unprovoked epileptic seizure or a status epilepticus from the time of diagnosis. The objective of the study was four-fold and subjects could participate in more than one of the substudies:

1. Worldwide, treatment policies differ after one unprovoked epileptic seizure. In some countries treatment is initiated after one seizure, while in other countries they have a wait-and-see policy. As many children have only one epileptic seizure during lifetime, treating them all would mean that many of them would be treated unnecessarily and would be exposed to the at times severe side effects of medication. In our country a wait-and-see policy was standard. We followed untreated children with only one epileptic seizure to study

the risk of a new seizure and its possible predictors (**First Seizure study**). A low risk of recurrence would justify the no-treatment policy after a first epileptic seizure, while a high risk would justify treatment of all patients. Further, in this study special attention was given to the accuracy and reliability of the diagnosis of a first epileptic seizure and the long-term outcome [34, 37, 38]. These first two aspects, which are mostly neglected in other studies, are important as the differential diagnoses of a single paroxysmal event are numerous and labeling a patient as having an epileptic seizure, while in fact is was not, or vice versa, may have great impact on both patient and family. Finally, children who entered the study with a status epilepticus - defined as a seizure with a duration of at least 30 minutes or recurrent seizures lasting a total of more than 30 minutes without regaining consciousness in between - were followed separately to study their long-term outcome [35]. Analyzing causes for status epilepticus, risk factors, recurrence rate and outcome including mortality after a status epilepticus may help to improve the immediate and long-term care for these children with epilepsy.

2. When children with epilepsy using anti-epileptic drugs reach remission, the question is how long a patient has to be seizure free before discontinuation of treatment is considered. Two studies (one from our country) showed that 75-80% of the children in whom medication was discontinued after two years reached a remission [91, 92]. Remarkably, in the study from Leiden, 90% of the children had a treatment response time - i.e. the interval between the start of medication and the beginning of the remission period - of less than two months [91]. Based on this, we hypothesized that a short treatment response time - and not so much the duration of remission - increases the chance of staying in remission after treatment discontinuation. In our study, children having a six-month remission period starting within two months after the beginning of treatment were regarded as fast-responders. They were randomized for either six or twelve months of treatment (**Short Treatment study**). We investigated whether a shorter treatment-duration in this group was possible without increasing the risk of recurrences [39].
3. Of all the children with epilepsy some have an inherent good prognosis, while others develop a chronic and therapy-resistant type of epilepsy. The question is if the first group needs to be exposed to the now and then severe side effects of anti-epileptic drugs, while in the second group the question is whether early intensive treatment might prevent therapy-resistance. Some investigators found that the intervals between successive untreated tonic-clonic seizures decreased, suggesting that there is an accelerating disease process in which seizures beget seizures, although in a later prospective study the decreasing pattern could not be affirmed [44]. Whether to delay or start treatment is a dilemma for the treating physician

in each individual patient. It would be valuable if a physician could accurately predict the long-term outcome of a patient in an early stage of the disease. In the **Prognosis study** which was part of the Dutch Study of Epilepsy we developed models to predict the two-year outcome based on information available at enrollment or on information that came available during the first six months of follow-up [41]. In a later stage we tested these models in a newly recruited cohort of children with epilepsy [93]. Further we studied the risk of mortality by comparing the death rate of our cohort with that of similar age-groups of the Dutch population in the same period [48].

4. The central nervous system interacts with the immune system and it might be possible that the immune system is involved in the pathogenesis of some types of epilepsy. Children with epilepsy might have abnormal serum immunoglobulin concentrations before treatment is started or at a later stage, in which case it is possible that these concentrations are caused by the use of some specific anti-epileptic drugs. Furthermore, it is possible that the serum immunoglobulin concentrations of children with a worse prognosis differ from those with a better prognosis. To investigate these aspects, serum samples of 282 unselected children of our cohort were taken before the start of medication and during the use of anti-epileptic drugs (**Immunology study**) [47].

This prospective cohort study - known as the Dutch Study of Epilepsy in Childhood -, was approved by the ethical committees of the participating hospitals and was financially supported by the Dutch National Epilepsy Fund (grants no. A72, A85, A86), and by the Princess Irene Fund Arnhem.

In 1988 we recruited all children aged one month to 16 years who attended hospital because of one or more epileptic episodes, had not been treated earlier for this, nor were referred from another hospital. Written informed consent was given by all parents and children of 12 years or older, not intellectually handicapped. All children were discussed in a panel of three neurologists. This panel had to decide whether the event or events were indeed of epileptic nature. Further, they had to classify the epileptic seizure and if possible - mostly in case of more seizures - the type of epilepsy and etiology. The discussions were based on the description of the episode of an eyewitness, and on the results of the EEGs or CT-scan if performed for the final classification. Two years after enrollment or after the start of medication all children were discussed again to see if the original diagnosis and classifications were still correct. Furthermore, they were classified using the ILAE classification that was not yet available at enrollment [94]. Children with a questionable diagnosis at enrollment were followed for one year to see if new events with a definite epileptic nature would

occur. In that case they were discussed again and included. After four years, enrollment stopped in 1992. **Figure 1.3** shows a flowchart of the included children. The recruitment rate of the original study approximated 75% of the expected annual incidence in the referral area of the participating hospitals.

After the diagnosis was made all children were regularly seen with intervals of three to six months. At each visit a form was completed with questions about the date and type of seizures, medication changes, and complaints, if applicable. Further, results of additional investigations like blood-plasma concentrations, liver functions, EEGs or CT-scans could be added.

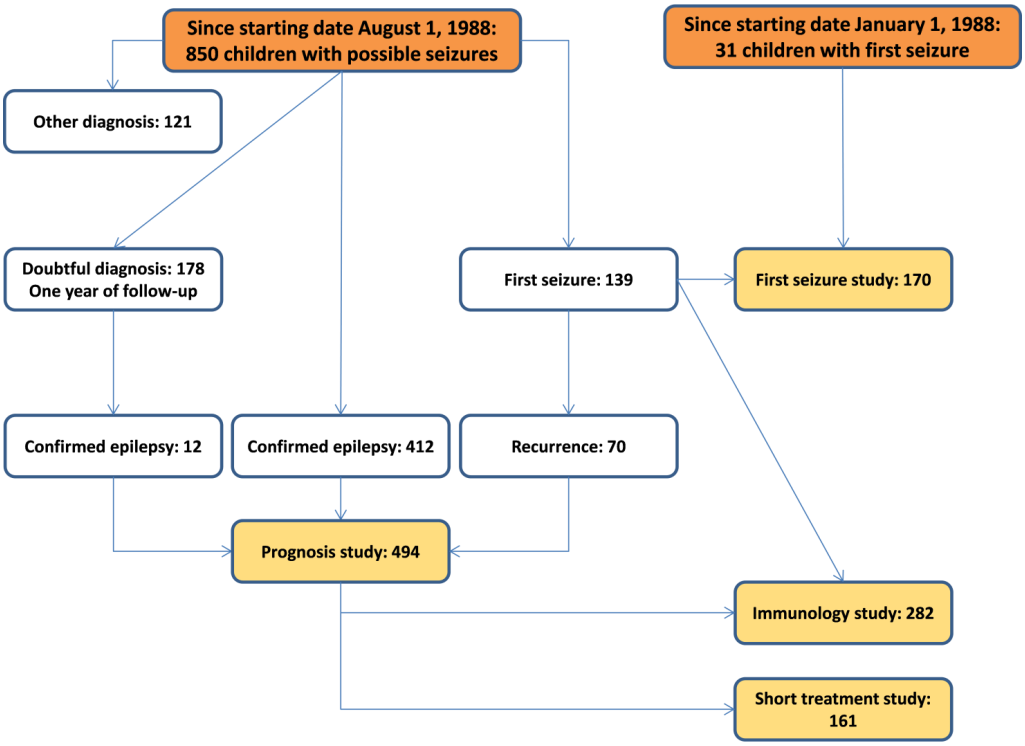
After the first five years with regular visits and contacts with patients, the follow-up of our cohort stopped. Later we decided to contact the cohort again, and between 2004 and 2006 we sent a questionnaire with items concerning epilepsy to 453 subjects with a five-year follow-up (**Appendix 1**). Questions included dates of last seizure, use of medication, dates of discontinuation of medication, health perception, other affections, disorders or restrictions due to epilepsy. We were also interested in the living arrangements of the subjects, and in addition their educational and occupational achievement. After some reminders and telephone contacts, 413 subjects returned their completed questionnaire. The response rate based on the original 494 subjects was 84%.

The main objective of the present thesis is to study the course and long-term outcome of childhood-onset epilepsy in terms of remission, intractability and mortality, as well as socioeconomic status. The second objective was to develop statistical models to be able to predict outcome for an individual person. By extending the follow-up of the original cohort, beside the long-term outcome, the consequences of epilepsy other than having seizures could be investigated.

Subjects in this cohort with a fast response to medication were randomized for either six months or twelve months of treatment (**Short Treatment study**). The objective of this trial was to investigate whether the duration of treatment could be reduced in fast responders without increasing the risk of new seizures. Their outcome at four years after randomization is described in **Chapter 2**.

Of the original cohort, 453 subjects had a follow-up of five years. The course of their epilepsy during these years is described in **Chapter 3 (Prognosis study)**. In addition, we present two models predicting the individual prognosis at five years of follow-up. One model is based on variables present at enrollment and the other on a combination of these variables and those derived during the first six months of follow-up.

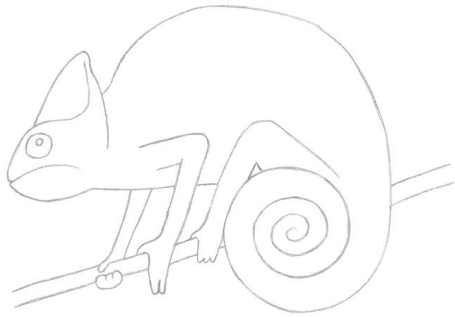
**Figure 1.3: Flowchart of 881 enrolled children with a possible first seizure or epilepsy**




About 10 years after the five-year follow-up, the 453 subjects mentioned above received a questionnaire for further research. Their course of epilepsy in terms of seizures and remission during a follow-up of almost 15 years is outlined in **Chapter 4**. This chapter also describes the mortality rate of the cohort during these years. Further, a combination of variables best predicting intractability is presented. **Chapter 5** describes the health aspects, restrictions, living arrangements, and socioeconomic status of the subjects as compared with age-peers of the Dutch population.

In our cohort, 9% of the subjects were intractable in the last year of follow-up, defined as having seizures in the last year of follow-up with remission periods of less than three months despite the use of adequate treatment. Because intractability is still a controversial issue in epilepsy, with different definitions used by several authors, we tried to depict the occurrence of intractability during the first five years of follow-up, time of onset, duration, and further course during the extended follow-up and made a comparison with intractability in the final year. We also tried to find explanations for the onset and discontinuation of intractability. The results of this investigation are presented in **Chapter 6**.

# Chapter 2 Four-year outcome after early withdrawal of antiepileptic drugs in childhood epilepsy



Ada.T. Geerts*; Jikkemien M.F. Niermeijer*; A.C.Boudewijn Peters; Willem Frans M. Arts; Oebele F. Brouwer; Hans Stroink; Els A.J. Peeters; and Cees.A. van Donselaar

*Neurology (2005), 64, 2136–2138*

*The first two authors contributed equally to this study.

## INTRODUCTION

Withdrawal of antiepileptic drugs is often considered in children with epilepsy who have remained seizure free for at least 2 years. While early withdrawal may prevent unnecessarily prolonged treatment, it may increase the risk of recurrence and a poor response to renewed treatment[1]; however, there are few data on the long-term outcome after recurrence.[2-6]

In an earlier prospective trial of early withdrawal (6 or 12 months) of antiepileptic drugs in children, the recurrence rate at 2 years after randomization was similar (49% versus 48%) in the two groups.[4] Here, we extended the follow-up to 4 years to determine which factors influence outcome and to develop a model to identify children who may benefit from early withdrawal.

## METHODS

The design and results of the 2-year follow-up study have been reported elsewhere.[4] Briefly, children aged between 1 month and 16 years with two or more unprovoked seizures or one status epilepticus who became seizure free within 2 months after starting treatment and remained so for 6 months were randomized to medication withdrawal at that time (6-month group) or after another 6 months of treatment (12-month group).

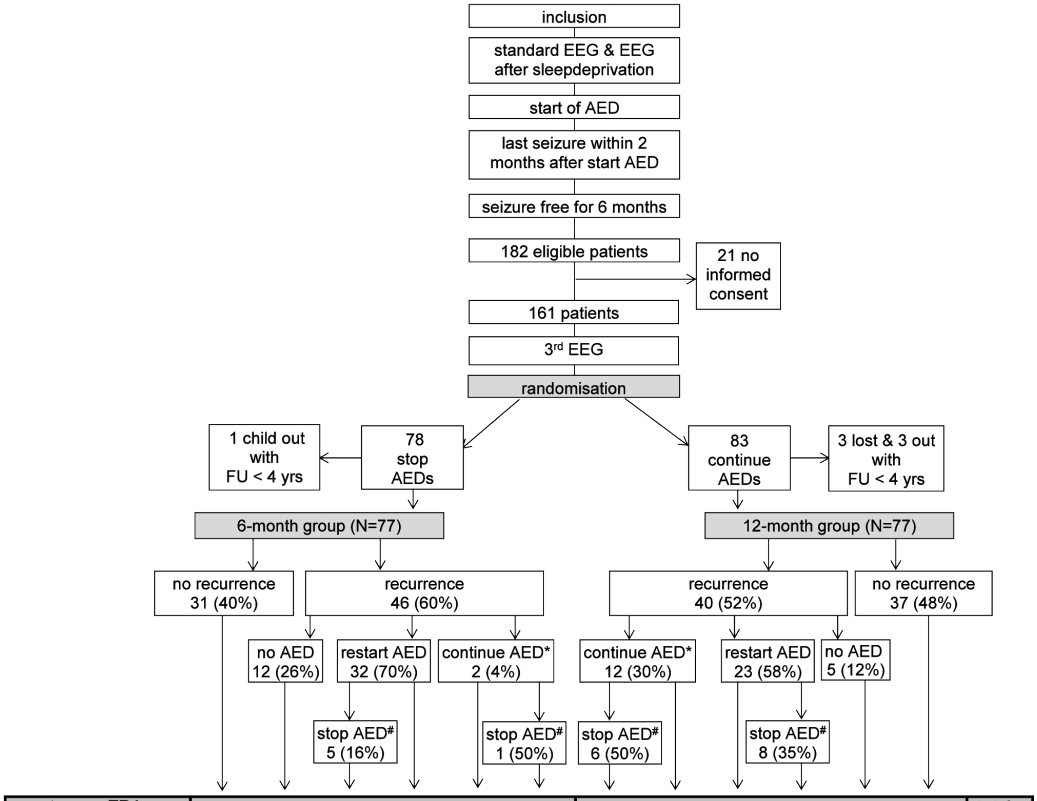
The first recurrence after randomization determined the recurrence rate and included recurrences occurring in the 12-month group before the planned withdrawal. We defined terminal remission as the interval between the last seizure and the last day of follow-up at 4 years after randomization (TR4). Outcome was excellent if a TR4 of at least 2 years was reached without medication during these 2 years.

Risk of recurrence was calculated using survival techniques and multiple logistic regression analysis. Missing values were derived by imputation. The goodness of fit of the final model was determined by the Pearson $\chi^2$ test. Bootstrapping techniques were used to test the internal validity of the model and to correct for over optimism. Regression coefficients were multiplied by the shrinkage factor (0.89) calculated from B = 10,000 bootstrap samples. A risk score (z) was derived and the chance of an excellent outcome was calculated using the formula: $p\ (\text{excellent}) = 1/(1 + e^{-z})$.

## RESULTS

We assessed the recurrence rate in 161 children and the 4-year outcome in 154 children; seven children with a limited follow-up after randomization were excluded (**Figure 2.1**).

**Figure 2.1: Study design, number of children analyzed, and the occurrence of first recurrences, medication use, and 4-year outcome in a randomized, prospective trial of children with newly diagnosed childhood epilepsy.**



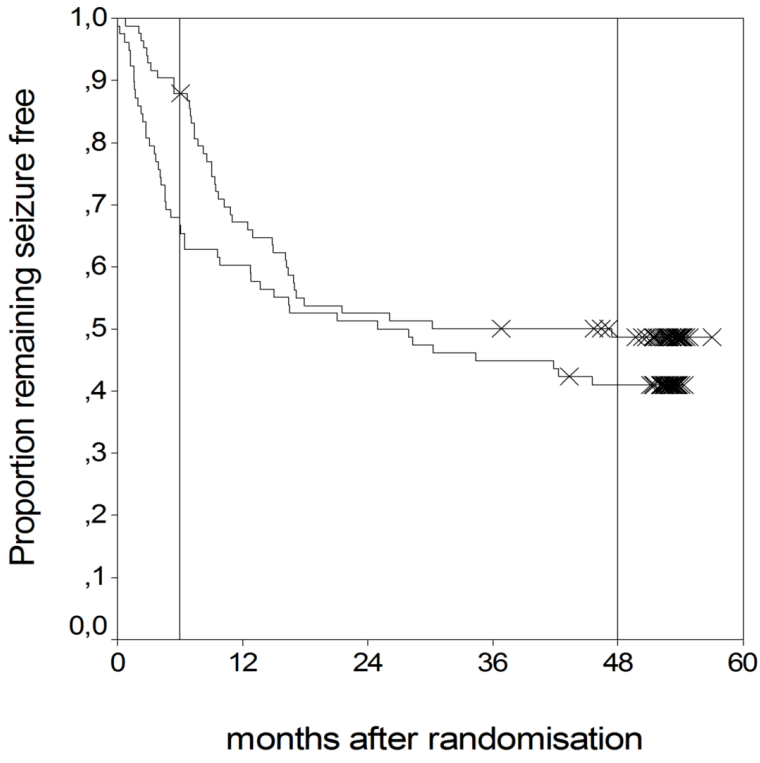

| outcome: TR4 | | | | | | | | | | | | totals: |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| >= 2 years, no AED during last 2 years | 31/77 (40%) | 6/77 (8%) | | | | | | | 1/77 (1%) | 3/77 (4%) | 37/77 (48%) | 78 (51%) |
| >= 2 years, with AED during last 2 years | | | 5/77 (6%) | 7/77 (9%) | | 1/77 (1%) | 3/77 (4%) | | 11/77 (14%) | 6/77 (8%) | | 33 (21%) |
| 1- 2 years with or without AEDs | | 4/77 (5%) | | 8/77 (10%) | 1/77 (1%) | | 2/77 (3%) | 2/77 (3%) | 2/77 (3%) | 1/77 (1%) | | 20 (13%) |
| < 1 year with or without AEDs | | 2/77 (3%) | | 12/77 (16%) | | | 1/77 (1%) | 4/77 (5%) | 2/77 (3%) | | 2/77 (3%) | 23 (15%) |

*Patients continued antiepileptic drug (AED) because a recurrence occurred during tapering or before the planned discontinuation of the AED.
#Discontinuation of AED before end of follow-up: 4 years after randomization.

Mean age at onset in the 154 children was 6.5 years (median 6.5 years); 76 (49.4%) were boys (**Table E-1** on the Neurology Web site at www.neurology.org or in **Appendix 2**).

Four years after randomization, 55% of the 161 children had a recurrence (**Figure 2.2**): 59% of the 6-month group and 51% of the 12-month group (95% confidence interval [CI] of the difference: -16% to 32%).

**Figure 2.2: Probability of remaining seizure free after immediate or delayed withdrawal of antiepileptic drug (AED) treatment in children with newly diagnosed epilepsy after 6 months of seizure freedom.**




| Months after randomization | 0 | 6 | 12 | 18 | 24 | 36 | 48 |
|---|---|---|---|---|---|---|---|
| At risk in 12-month group | 83 | 72 | 55 | 44 | 43 | 41 | 36 |
| At risk in 6-month group | 78 | 72 | 47 | 41 | 40 | 35 | 31 |

Kaplan–Meier curves: lower curve = 6-month group (n = 78), upper curve = 12-month group (n = 83). Xs in curves represent censored children. Test statistics (log-rank) for equality of the two survival distributions was 1.83 (df = 1, p = 0.1756).

Recurrence rates were equal at 2 years of follow-up, but the 6-month group had relatively more late recurrences. If only the children who had no seizures during the first 2 years after randomization were considered, the 6-month group had a recurrence rate at 4 years of 20% vs 7% in the 12-month group: (95% CI of the difference: -4 to 29%). Similar results were obtained if recurrence rates were calculated from the time medication was stopped instead of randomization.

Seventy-eight of the 154 (51%) children had an excellent outcome (44% without and 7% after a recurrence); 33 (21%) had a TR4 of 2 years or more with medication during at least a part of these 2 years; 23 (15%) had a TR4 of less than 1 year (**Figure 2.1**). Differences between the 6-month and the 12-month groups were not significant. Of the 55 children who restarted medication, 14 (25%) experienced seizure recurrence. Adverse events or death did not occur during the study period. Two children experienced a status epilepticus after withdrawal (one in each group). One child continued to have seizures despite restarting medication, whereas the other remained seizure free.

In the univariate analyses, duration of initial treatment was not significantly associated with outcome, whereas age at onset, number of seizures before start of medication, seizure and epilepsy type, etiology, EEG findings, and postictal signs before study inclusion were (**Table E-1** on the Neurology Web site at www.neurology.org or in **Appendix 2**). These variables, except for number of seizures and epilepsy type, remained in the final predictive model (**Table E-2** on the Neurology Web site at www.neurology.org or in **Appendix 2**). The sensitivity (69.2%) and specificity (76.3%) were highest at a cutoff *p* value of 0.63 (positive predictive value = 75.0%; negative predictive value = 70.7%). *p* Values above the cutoff point indicate an excellent outcome. Receiver operating characteristics revealed an area under the curve of 0.78. The model correctly classified 10 of the 12 children (83%) with a predicted chance of a good outcome of <25%, 67 of the 100 (67%) with a predicted chance of a good outcome of 25 to 75%, and 35 of the 42 (83%) with a predicted chance of a good outcome of >75%. Overall, the model correctly classified 72.7% of the children. The chance of an excellent outcome for various combinations of predictive factors is given in **Table 2.1**.

## DISCUSSION

We extended the follow-up period of our earlier clinical trial of early withdrawal of medication in children with epilepsy with a rapid response to antiepileptic drugs.[4] In that study, the rate of recurrence at 2 years was similar between groups in which medication was withdrawn after 6 or 12 months. In the current study, recurrence rates at 4 years after randomization were not significantly different (59% versus 51%), but the 6-month group had relatively more recurrences during the last 2 years of follow-up. The relatively longer follow-up period of the 6-month group after medication withdrawal did not explain this difference. However, we cannot exclude that the shorter treatment

**Table 2.1: Calculated chances (%) of an excellent outcome in children with epilepsy who respond to treatment within 2 months after start of AEDs and remain seizure free for 6 months**

| | Age at onset, y | |
|---|---|---|
| Seizures | <6 | ≥6 |
| Absence (chance, %) | 87 | 78 |
| No absence (chance, %) | | |
| Normal EEG (no post-ictal signs) | | |
| Idiopathic | 87 | 78 |
| Non-idiopathic | 78 | 66 |
| Normal EEG (post-ictal signs) | | |
| Idiopathic | 60 | 44 |
| Non-idiopathic | 45 | 30 |
| Abnormal EEG (no post-ictal signs) | | |
| Idiopathic | 63 | 48 |
| Non-idiopathic | 48 | 34 |
| Abnormal EEG (post-ictal signs) | | |
| Idiopathic | 28 | 17 |
| Non-idiopathic | 18 | 10 |

All combinations of variables based on the predictive multivariate model are shown. Confidence intervals after shrinkage cannot be calculated but will be wide for most estimates.

was responsible for these late recurrences. The overall recurrence rate of 55% at 4 years after randomization is higher than that of other studies, probably because of patient selection. While most withdrawal studies included only children who had been seizure free for 2 years, thereby excluding children with a poorer prognosis, we included such children.

Outcome after early withdrawal was excellent in 51% of the children. These children had a terminal remission of at least 2 years without medication, and hence unnecessary treatment was prevented for 12 to 18 months. There were no adverse effects. However, 15% of children had a TR4 shorter than 1 year and 25% did not become seizure free after restarting medication. Failure of renewed treatment may be a serious risk of early withdrawal, but our results are comparable with those of other studies of withdrawal after at least 2 years of treatment.[2,3,6] Moreover, children on continuous medication may also have recurrences during longer follow-up.[7]

We found that age at onset younger than 6 years, idiopathic etiology, having only absences, lack of postictal signs, and normal EEG findings were significant predictors of an excellent outcome, as reported previously[1-3,8-10] and are comparable with indicators for good outcome of childhood epilepsy in general.[7] Thus, it may be more appropriate to consider in which patients medication can be stopped safely than when medication can be stopped. Our model had a fair validity in predicting which children would have an excellent outcome, but the clinical validity of the model should be tested further.

We did not compare early withdrawal with the standard withdrawal protocol (2-year seizure-free interval) and hence cannot comment on the possible (dis)advantages of early withdrawal. While we cannot recommend early withdrawal in all children with a rapid response to antiepileptic medication, our findings suggest that early withdrawal should be considered in a large proportion of such children. Our predictive model discriminated between children with a good versus poor chance of attaining an excellent outcome.

**ACKNOWLEDGMENT**

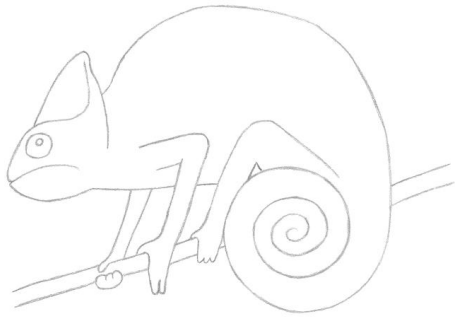
The authors thank Cuno Uiterwaal for comments on the final manuscript.

**REFERENCES**

1. Sirven JI, Sperling M, Wingerchuk DM. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev 2001:CD001902.
2. Todt H. The late prognosis of epilepsy in childhood: results of a prospective follow-up study. Epilepsia 1984;25:137–144.
3. Matricardi M, Brinciotti M, Benedetti P. Outcome after discontinuation of antiepileptic drug therapy in children with epilepsy. Epilepsia 1989;30:582–589.
4. Peters AC, Brouwer OF, Geerts AT, Arts WF, Stroink H, van Donselaar CA. Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy. Neurology 1998;50:724–730.
5. Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. J Pediatr 1993;122:861–868.

6. Bouma PA, Peters AC, Brouwer OF. Long term course of childhood epilepsy following relapse after antiepileptic drug withdrawal. J Neurol Neurosurg Psychiatry 2002;72:507–510.
7. Arts WF, Brouwer OF, Peters AC, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 2004;127:1774–1784.
8. Arts WF, Visser LH, Loonen MC, et al. Follow-up of 146 children with epilepsy after withdrawal of antiepileptic therapy. Epilepsia 1988;29:244–250.
9. Shinnar S, Berg AT, Moshe SL, et al. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. Ann Neurol 1994;35:534–545.
10. Dooley J, Gordon K, Camfield P, Camfield C, Smith E. Discontinuation of anticonvulsant therapy in children free of seizures for 1 year: a prospective study. Neurology 1996;46:969–974.

# Chapter 3 Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood



Willem Frans M. Arts, Oebele F. Brouwer, A.C. Boudewijn Peters, Hans Stroink, Els A.J. Peeters, Paul I.M. Schmitz, Cees A. van Donselaar, and Ada T. Geerts

*Brain (2004), 127, 1774–1784*

**ABSTRACT**

Knowing the prognosis of epilepsy will undoubtedly influence the treatment strategy. This study aimed to define the prospects of newly diagnosed childhood epilepsy, assess the dynamics of its course, identify relevant variables and develop models to assess the individual prognosis. Four hundred and fifty-three children with newly diagnosed epilepsy were followed for 5 years. Terminal remission at 5 years (TR5) was compared with terminal remission at 2 years (TR2) and with the longest remission during follow-up. Variables defined at intake and at 6 months of follow-up were analyzed for their prognostic relevance. In multivariate analyses, combinations of variables were tested to develop reliable models for the calculation of the individual prognosis. Data on treatment, course during follow-up and epilepsy syndromes were also studied. Three hundred and forty-five children (76%) had a TR5 >1 year, 290 (64%) >2 years and 65 (14%) had not had any seizure during the entire follow-up. Out of 108 children (24%) with TR5 <1 year, 27 were actually intractable at 5 years. Medication was started in 388 children (86%). In 227 of these (59%), anti-epileptic drugs (AEDs) could be withdrawn. A TR5 >1 year was attained by 46% on one AED, on the second AED by 19%, and by 9% on all additional AED regimes. Almost 60% of the children treated with a second or additional AED regime had aTR5>1 year. Variables predicting the outcome at intake were etiology, history of febrile seizures and age. For intake and 6-month variables combined, sex, etiology, postictal signs, history of febrile seizures and TR at 6 months were significant. The model derived from intake variables only predicted TR5 <1 year correctly in 36% and TR5 >1 year in 85% (sensitivity 0.65, specificity 0.64). The corresponding values for the model derived from intake and 6-month variables were 43 and 88% (sensitivity 0.69, specificity 0.71). The course of the epilepsy was constantly favorable in 51%, steadily poor in 17%, improving in 25% and deteriorating in 6%. Intractability was in part only a temporary phenomenon. The outcome at 5 years in this cohort of children with newly diagnosed epilepsy was favorable in 76%; 64% were off medication at that time. Almost a third of the children had a fluctuating course; improvement was clearly more common than deterioration. After failure of the first AED, treatment can still be successful. Models predicting the outcome have fewer misclassifications when predicting a long terminal remission than when predicting continuing seizures.

**Abbreviations**

AED = anti-epileptic drug; CI = confidence interval; DSEC = Dutch Study of Epilepsy in childhood; LR = longest remission during a defined period of follow-up; OR = odds ratio; RC = regression coefficient; ROC = receiver operant characteristic; TR = length of terminal remission

existing at moment of evaluation; TR2 = terminal remission existing at 2 years; TR5 = terminal remission existing at 5 years.

## INTRODUCTION

The prognosis of childhood epilepsy has important epidemiological and clinical implications. Assessment of the risk profile of an individual patient may be used to tailor the treatment strategy. Not initiating anti-epileptic drug (AED) treatment after a first unprovoked seizure is now an evidence-based established practice (Hirtz et al., 2003). Conversely, decisions whether and, if so, when to start treatment in children with epilepsy are not based on firm clinical evidence since trials comparing different treatment strategies are lacking. Randomized studies to explore the way in which AEDs influence the natural course of epilepsy are usually considered unethical. The only exception so far is the Multicenter Study of Early Epilepsy and Single Seizures (MESS) trial, conducted in the UK, of which results will be available shortly. Although in recent years the opinion that AEDs only suppress seizures and have no influence on the course of the disease (Shinnar and Berg, 1996) has gained momentum, some authors have maintained that early vigorous treatment is essential to prevent intractability (Reynolds et al., 1983). The possibility of a self-perpetuating mechanism of untreated epileptic seizures (Gowers, 1881; Reynolds et al., 1983; opposed by van Donselaar et al., 1997) is in contrast with the results of large cohort studies indicating that about 60% of children with newly diagnosed epilepsy have a good prognosis (Camfield et al., 1993; Sillanpää et al., 1998). To resolve the controversy, it remains essential to gather entirely, prospective follow-up data in large cohorts of patients of all ages with different types of epilepsy, look for evidence adding to the already available knowledge, and develop instruments to assess the prognosis of an individual patient. This might ultimately provide a sound medical and ethical basis for trials addressing the issue more directly.

The Dutch Study of Epilepsy in Childhood (DSEC) provides some of the answers needed. We prospectively studied a cohort of children with newly diagnosed epilepsy, determined their outcomes, and identified factors associated with good and poor seizure outcomes. We also studied the dynamics of the course of the epilepsy and addressed the question of when and how to define intractability. Another goal was to identify children with newly diagnosed epilepsy who might benefit from immediate and vigorous treatment because of their poor prognosis, or in whom treatment could possibly be withheld or at least postponed because of the inherently favorable prognosis. In this paper, we present the data of the 5-year follow-up of the cohort, following up on our analysis of the 2-year outcome (Arts et al., 1999).

## METHODS

### Composition of the cohort

The design of the study and the results of the 2-year follow-up have been described previously (Arts et al., 1999). A hospital-based cohort (n = 466) of children aged 1 month to 15 years with newly diagnosed epilepsy (defined as two or more unprovoked seizures within a 1-year period) was recruited after informed consent of the parents. Four Dutch hospitals participated: two University hospitals (Rotterdam and Leiden), one children's hospital and one general hospital (both in The Hague). The cohort comprised about 75% of the expected incidence in their referral areas. The attending pediatric neurologist completed an extensive questionnaire on the description of the event(s), possible provoking factors, previous medical history and the family history. Confirmation of the diagnosis of epilepsy by a committee of three pediatric neurologists, using predefined diagnostic criteria, was required for inclusion. The etiology was classified according to the definitions of the International League Against Epilepsy (ILAE; Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993) as idiopathic, cryptogenic or remote symptomatic. The etiology of children with mental retardation was classified as remote symptomatic. Children with acute symptomatic seizures only were excluded. Epilepsy types and syndromes were classified according to the International Classification of Epilepsies and Epileptic Syndromes (ICES; Commission on Classification and Terminology of the International League Against Epilepsy, 1989). This was done at 2 years of follow-up, because the ICES had not yet been published when we started the study.

### Follow-up and outcome

The follow-up of the original cohort (n = 466) was extended until 5 years after intake. We chose a fixed duration of follow-up for all children (instead of a variable length) to facilitate outcome comparisons at fixed intervals (6 months, 2 years, 5 years) and to examine the course of the epilepsy of all children during the entire follow-up.

Eight children died during the 5-year follow-up (Callenbach et al., 2001). They were not included in the present analyses. Five children (1.1%) were lost. Eventually, 453 patients remained for the analyses at 5 years.

We defined outcome as terminal remission (TR): the time from the last seizure to the moment of evaluation (i.e. 2 and 5 years after study entry). The TR at 5 years (TR5) was trichotomized (<1 year, 1–2 years, >2 years).We defined intractability at 2 and 5 years as a TR <1 year and longest remission (LR) <3 months during the last year of observation despite adequate treatment

(Huttenlocher and Hapke, 1990; Berg et al., 2001; A. Berg, personal communication). Adequate treatment was defined as the optimal use of at least two AEDs, either alone or in combination. The course during the follow-up was compared with TR5 in two ways. First, we compared TR5 with TR2. Next, we studied the duration of the LR during the entire 5-year follow-up in relation to the occurrence of seizure(s) during the last year of follow-up (TR5 <1 year).

**Treatment**

Treatment decisions were made by each child's treating pediatric neurologist. In children who needed AED treatment, we tried at least two first-choice AEDs in monotherapy (mostly sodium valproate and carbamazepine) before using a polytherapy regimen. In children who experienced long-term remission, we usually withdrew the AED(s) after 2 years without seizures. However, our cohort also contained 161 children in whom medication was withdrawn much earlier, selected on the basis of a rapid and complete response to AED therapy (Peters et al., 1998).

**Determinants**

A priori-defined variables, including EEG, were collected at intake and at 6 months of follow-up (**Table 3.1**). These possible determinants were analyzed for their relevance for the outcome at 2 years (Arts et al., 1999) and 5 years after intake (see below). In the univariate analysis, age at intake was categorized in five groups (0–3, 3–6, 6–9, 9–12 and 12–16 years of age) to show more detail. In the multivariate analyses, age as a continuous variable was analyzed both on linear and transformed scales to determine which scale best predicted the outcome. Since none of these was satisfactory, age was dichotomized (below and above 6 years of age). This also reduced the number of dummy variables.

The temporal seizure pattern before intake (**Table 3.1**) was studied as a possible determinant on the basis of a report by Shorvon (1984). We identified the following patterns: continuous (intervals between seizures <1 week); intermittent (intervals between seizures >1 week); multiple bursts (clusters of seizures within one week with >1 week between the clusters); status epilepticus (seizure with duration of >30 min); solitary burst (one cluster of seizures within a period of at most 1 week).

**Statistical analyses**

The correlation of intake and 6-month follow-up determinants with outcome (defined as TR5 less than or more than 1 year) was analyzed with a modelling strategy (Harrell et al., 1996). When variables had missing values (e.g. family history), these were derived using imputation. Variables with many missing values (e.g. CT) were not considered in the multivariate analyses. After a stable model had been established, all second-order interaction terms of each determinant remaining in the

model were tested. Significant interaction terms were added to the model. The goodness of fit of the models was determined by Pearson's $\chi^2$ test. Bootstrapping techniques were used to determine the internal validity of the final models.

For each group that we analyzed, we developed a model with intake variables only and a model with intake and 6-month variables combined.

From the odds ratios of the variables contributing to these models, regression coefficients (RC) can be derived. For each individual patient, the RCs of the applicable variables and a constant for the model can be summated to obtain the individual's sum score. From the sum score, the predicted probability of a poor outcome can be calculated using the formula $P = 1/1+e^{-Z}$, in which Z is sum score/–100. The area under the receiver operant characteristic (ROC) curve (giving the relation between the sensitivity and the specificity of the predictions) is a measure of the ability of the model to discriminate between patients with and without a poor outcome. The value of P with the best combination of sensitivity and specificity is the probability cut-off. Any value of P above the cut-off predicts TR5 <1 year; any value below P predicts the opposite. Since P can be plotted against Z and, therefore, also against the sum score, one can use the sum score for the determination of the individual's prognosis. The cut-off value of P directly yields a cut-off value of Z and the sum score. Using the individual's value of the sum score (below or above the cut-off) facilitates the use of the model in daily clinical practice.

## RESULTS

### Outcome

Of the 453 children, 345 (76%) attained a TR5 of at least one year, 290 (64%) of at least 2 years and 248 (55%) had not had any seizure since the 2-year outcome evaluation (**Figure 3.1**). The moment of entering TR5 (i.e. the day of the last seizure during the 5-year follow-up) is presented as a Kaplan-Meier survival curve in **Figure 3.2**. It shows that half of the cohort had reached terminal remission after 18.5 months of follow-up.

Sixty-five children (14%) were completely seizure free since the intake (**Figure 3.1**). In the univariate analyses, a number of significant variables distinguished this group from the 388 children with seizures after intake. They had had fewer seizures before intake, more often of a generalized tonic-clonic nature. Their EEG showed less often epileptiform discharges and they less often had symptomatic epilepsy. Their seizure pattern had more often been intermittent or a single burst and less often continuous.

Twenty-seven (6%) out of 108 children (24%) with a TR5 of less than one year fulfilled our criteria for intractability. Of these, seven children had symptomatic partial and seven others cryptogenic

partial epilepsy; five had cryptogenic generalized and one symptomatic generalized epilepsy. Three had been classified as idiopathic generalized epilepsy with (mainly) absences, and four as idiopathic generalized epilepsy with (mainly) generalized tonic-clonic seizures.

**Figure 3.1: Outcome of 453 children with newly diagnosed epilepsy at 5 years of follow-up**

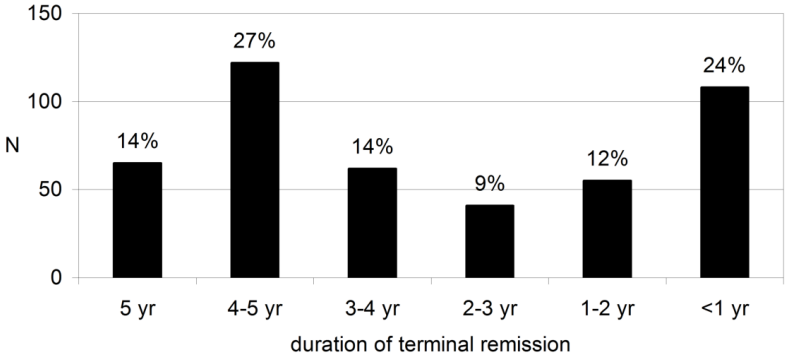
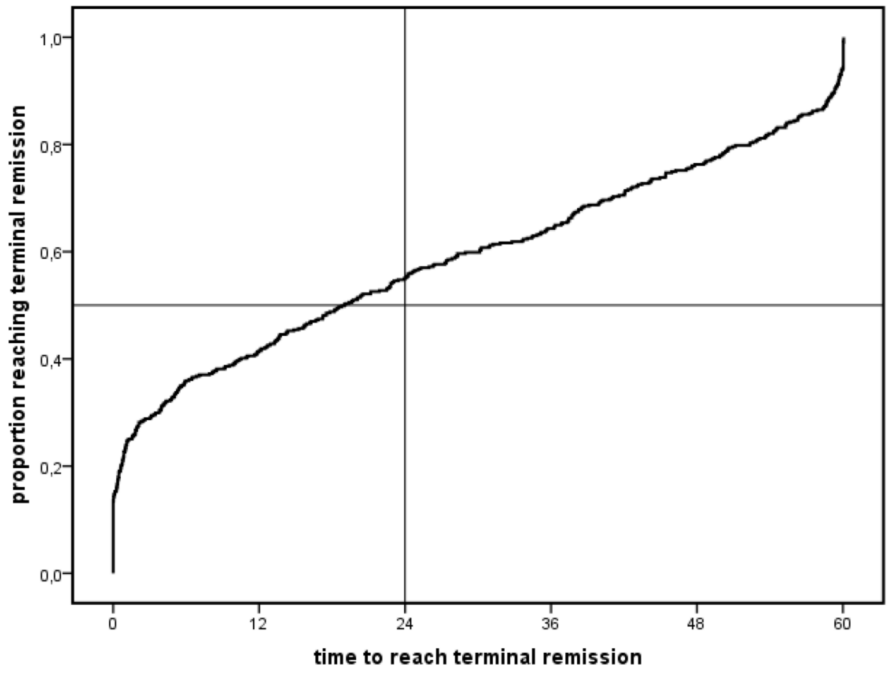



**Figure 3.2: Moment (time in months) of the last seizure before entering the terminal remission existing at 5 years of follow-up for 453 children in the cohort. Kaplan–Meier survival curve**



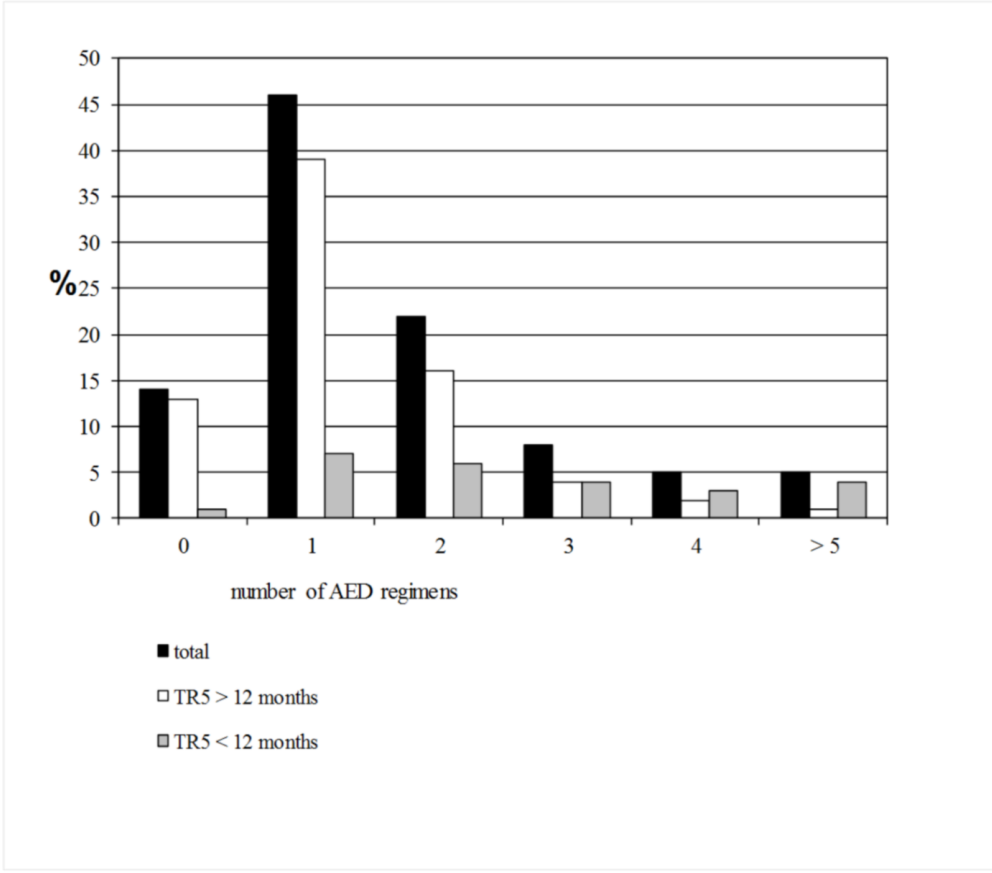
**Treatment**

Sixty-five children (14%) were not treated with AEDs. Most of these suffered from sporadic generalized tonic-clonic seizures. Of the 65 untreated children, 61 (94%) achieved a TR5 >1 year, and 53 (82%) > 2 years.

Medication was prescribed to 388 (86%) children. Of these, 206 (53%) received only one AED and 182 (47%) two or more (up to nine) AEDs or AED regimens (**Figure 3.3**). Of the 388 treated children, 46% attained a TR5 >1 year on one AED, 19% reached this end-point on two AED regimes and 9% on three or more.

Medication was withdrawn in 227 (59% of 388 treated) patients of whom 13 had a TR5 less than one year and 214 a TR5 of >1 year. At 5 years of follow-up, 161 (36% of 453) patients were still using AEDs (TR5 <1 year: 91; TR5 >1 year: 70).

**Figure 3.3: Number of anti-epileptic drug (AED) regimens during 5 years of follow-up in the entire cohort and in each of two 5-year outcome categories, all expressed as percentage of the entire cohort (n = 453)**



**Predictive variables**

The determinants of seizure outcome at 5 years were largely identical to those found in the 2-year analysis (**Table 3.1**).

**Table 3.1: Univariate analysis**

| | Number of children | % with TR2 <1 year | % with TR5 <1 year | OR for TR5 <1 year (95% CI's) |
|---|---|---|---|---|
| **INTAKE** | | | | |
| Overall | 453 | 43 | 24 | |
| Sex | | | | |
| - Male | 221 | 42 | 22 | 1.00 |
| - Female | 232 | 44 | 26 | 1.26 (0.81, 1.94) |
| Age at intake (years) | | | | |
| - 0 – 3 | 145 | 48 | 28 | 1.00 |
| - 3 – 6 | 90 | 46 | 30 | 1.13 (0.63, 2.01) |
| - 6 – 9 | 99 | 39 | 15 | 0.47 (0.24, 0.91)* |
| - 9 – 12 | 73 | 34 | 18 | 0.57 (0.28, 1.15) |
| - 12 – 16 | 46 | 41 | 28 | 1.03 (0.49, 2.17) |
| No. of seizures before intake | | | | |
| - < 25 | 285 | 42 | 22 | 1.00 |
| - > 25 | 168 | 44 | 26 | 1.23 (0.79, 1.91) |
| Seizure type | | | | |
| - Generalized tonic-clonic | 272 | 38 | 22 | 1.00 |
| - Complex partial | 49 | 51 | 35 | 1.88 (0.97, 3.63) |
| - Simple partial | 29 | 69 | 17 | 0.74 (0.27, 2.02) |
| - Absences | 59 | 32 | 19 | 0.81 (0.40, 1.66) |
| - Infantile spasms, myoclonic/ atonic seizures, etc. | 44 | 57 | 34 | 1.83 (0.92, 3.65) |
| Type of epilepsy | | | | *** |
| - Generalized idiopathic | 193 | 32 | 16 | 1.00 |
| - Generalized cryptogenic | 31 | 52 | 42 | 3.92 (1.70, 9.06)*** |
| - Generalized symptomatic | 32 | 47 | 28 | 2.13 (0.89, 5.08) |
| - Partial idiopathic | 28 | 39 | 0 | 0.00 |
| - Partial cryptogenic | 86 | 48 | 34 | 2.76 (1.51, 5.07)*** |
| - Partial symptomatic | 67 | 63 | 39 | 3.45 (1.80, 6.59)*** |
| - Unclassifiable | 16 | 38 | 6 | 0.36 (0.05, 2.87) |
| Etiology | | | | *** |
| - Idiopathic | 232 | 33 | 14 | 1.00 |
| - Remote symptomatic | 126 | 56 | 33 | 2.91 (1.70, 4.98)*** |
| - Cryptogenic | 95 | 48 | 36 | 3.36 (1.89, 5.98)*** |
| Pre-existing neurological signs | | | | |
| - Absent | 396 | 41 | 22 | 1.00 |
| - Present | 57 | 54 | 33 | 1.72 (0.94, 3.15) |
| Postictal signs | | | | |
| - Absent | 407 | 42 | 22 | 1.00 |

| | Number of children | % with TR2 <1 year | % with TR5 <1 year | OR for TR5 <1 year (95% CI's) |
|---|---|---|---|---|
| - Present | 46 | 52 | 39 | 2.26 (1.19, 4.30)* |
| History of febrile convulsions | | | | |
| - No | 406 | 42 | 23 | 1.00 |
| - Yes | 47 | 51 | 32 | 1.58 (0.82, 3.04) |
| Family history | | | | |
| - Negative | 395 | 44 | 24 | 1.00 |
| - Positive | 58 | 31 | 24 | 1.02 (0.53, 1.94) |
| Standard intake EEG | | | | |
| - Normal | 111 | 36 | 20 | 1.00 |
| - Epileptiform | 267 | 45 | 25 | 1.32 (0.76, 2.27) |
| - Other abnormalities | 69 | 45 | 28 | 1.54 (0.76, 3.13) |
| CT scan | | | | |
| - Normal | 245 | 40 | 24 | 1.00 |
| - Abnormal | 67 | 61 | 34 | 1.69 (0.94, 3.03) |
| - Not obtained | 141 | 38 | 19 | 0.76 (0.46, 1.28) |
| Temporal seizure pattern | | | | |
| - Continuous | 189 | 41 | 25 | 1.00 |
| - Intermittent | 162 | 43 | 19 | 0.71 (0.43, 1.20) |
| - Multiple bursts | 17 | 59 | 47 | 2.69 (0.97, 7.45)* |
| - Solitary status epilepticus | 24 | 46 | 33 | 1.51 (0.61, 3.77) |
| - Solitary burst | 61 | 39 | 23 | 0.90 (0.45, 1.78) |
| | | | | |
| **6 MONTHS AFTER INTAKE** | | | | |
| No. of seizures within 6 months | | | | |
| - < 25 | 288 | 40 | 21 | 1.00 |
| - > 25 | 165 | 47 | 27 | 1.56 (1.00, 2.43)* |
| 3-month remission ever in 6 months | | | | |
| - No | 123 | 67 | 42 | 1.00 |
| - Yes | 330 | 34 | 17 | 0.28 (0.17, 0.45)*** |
| 6-month EEG | | | | |
| - Normal | 122 | 32 | 17 | 1.00 |
| - Epileptiform | 110 | 55 | 32 | 2.24 (1.20, 4.21)** |
| - Other abnormalities | 58 | 43 | 24 | 1.53 (0.71, 3.30) |
| - Not obtained | 163 | 42 | 23 | 1.46 (0.81, 2.66) |
| TR at 6 months | | | | |
| - 6 months | 141 | 28 | 13 | 1.00 |
| - 2 to 6 months | 171 | 38 | 17 | 1.46 (0.77, 2.74) |
| - 0 to 2 months | 141 | 51 | 43 | 5.23 (2.77, 9.89)*** |

The table shows the distribution of the possible determinants collected at intake and after 6 months, percentages of children with a TR2 and TR5 <1 year and odds ratios for TR5 <1 year for each value of the intake and 6-month variables compared with the reference value of that variable, scored as 1.00. OR = odds ratio; CI = confidence interval. *P < 0.05; **P < 0.01; ***P < 0.001.

Few variables showed substantial changes in outcome when the TRs at 2 and 5 years were compared. Most conspicuously, patients with simple partial seizures had a significantly worse outcome at 2 years in comparison with patients with generalized tonic–clonic seizures, but at 5 years of follow-up their outcome was better, although not significantly so.

Multivariate analyses of the 5-year outcome with logistic regression models are presented in **Table 3.2A**. The model with intake variables only retained sex, age at intake, initial EEG, etiology, history of febrile seizures and postictal signs. Etiology and history of febrile seizures interacted.

**Table 3.2A: Multivariate analyses**

| | **Intake variables** | **Intake and 6-month variables** |
|---|---|---|
| Number of children | 453 | 453 |
| Number of covariate patterns | 43 | 119 |
| Pearson $\chi^2$ (74) | 35.30 | 93.63 |
| Probability > $\chi^2$ | 0.45 | 0.84 |
| Area under ROC curve | 0.70 | 0.77 |
| | | |
| **VARIABLES** | **OR (95% CI)** | **OR (95% CI)** |
| Sex (male/female) | 1.49 (0.93, 2.37) | 1.64 (1.00, 2.70)* |
| Age at intake (<6/≥ 6 years) | 0.62 (0.39, 0.99)* | 0.87 (0.52, 1.43) |
| EEG at intake (normal/abnormal) | 1.34 (0.77, 2.34) | |
| Etiology (idiopathic/not idiopathic) | | |
| *If no febrile seizures occurred* | 3.72 (2.20, 6.30)*** | 3.58 (2.05, 6.27)*** |
| *If febrile seizures occurred* | 0.63 (0.17, 2.30) | 0.56 (0.14, 2.18) |
| History of febrile seizures (no/yes) | | |
| *If etiology is idiopathic* | 4.37 (1.70, 11.26)** | 5.28 (1.92, 14.51)*** |
| *If etiology is non-idiopathic* | 0.74 (0.27, 2.08) | 0.82 (0.28, 2.4) |
| Postictal signs (no/yes) | 1.83 (0.93, 3.60) | 2.23 (1.08, 4.63)* |
| No. of seizures in 1st 6 months (< 25/>25) | | 0.77 (0.42, 1.41) |
| 3-month remission (no/yes) | | 0.58 (0.29, 1.13) |
| Terminal remission at 6 months | | |
| 6 months (no/yes) | | 1.00 |
| 2 to 6 months (no/yes) | | 1.57 (0.78, 3.17) |
| 0 to 2 months (no/yes) | | 4.47 (2.00, 9.99)*** |

The table shows odds ratios (OR) and 95% confidence intervals (CI) for the models with intake variables only and with intake and 6-month variables for a terminal remission (TR5) of <1 year at 5 years of follow-up. Logistic regression model with interaction according to Harrell et al., 1996.
*P < 0.05; **P < 0.01; ***P < 0.001.

Children with cryptogenic or remote symptomatic etiology without a history of febrile convulsions had a worse prognosis than those with idiopathic etiology and no febrile convulsions. On the other hand, a history of febrile convulsions was a significant predictor of a worse outcome in all children with idiopathic epilepsy, but not in the children with non-idiopathic epilepsy. The model with intake and 6-month variables combined retained the above variables except for the initial EEG, and, in addition, the number of seizures and the longest remission during the first 6 months of follow-up, and the duration of terminal remission at 6 months. The following variables attained significance. The outcome was worse for girls than for boys, as well as in children with postictal signs, a TR at 6 months of <2 months, non-idiopathic etiology and a history of febrile seizures. Again we found a significant interaction between etiology and febrile convulsions.

Based on the models presented here, it is possible to determine the individual prognosis of children with newly diagnosed epilepsy by calculating the sum score (**Table 3.2B**). In these models, the value of the sum score for an individual reflects his or her chance of having a TR5 <1 year. In the model with intake variables only, the sum score cut-off equals 110, which is derived from P = 0.25. This P value corresponds to the best combination of sensitivity (0.65) and specificity (0.64), resulting in a predictive value for TR5 <1 year of 0.36 and predictive value for TR5 >1 year of 0.85. The interpretation of these figures is that for sum scores more than 110, a TR5 >1 year is predicted with few false predictions (15%). However, the prediction of TR5 <1 year (sum score lower than 110) yields a large number of false predictions (64%). The number of misclassifications amounts to 38 (false prediction of TR5 >1 year) + 124 (false prediction of TR5 <1 year) = 162 (36%).

For the model with intake and 6-month variables combined, the sum score cut-off equals 132 derived from a P = 0.21. The resulting values for sensitivity, specificity, positive and negative predictive value are 0.69, 0.71, 0.43 and 0.88. One can see that this model is more reliable than the one with intake variables only, but suffers from the same deficit: too many false predictions of TR5 <1 year. The number of misclassifications amounts to 33 + 101 = 134 (30%). A simplified way of calculating the individual prognosis with the help of these data is given in **Table 3.2B**.

For children with a defined epilepsy syndrome, it may not be necessary to use a complicated model to determine the prognosis, because the syndrome itself largely determines the prognosis. Therefore, we analyzed the group that remained after removal of all children with a well-defined epilepsy syndrome and with idiopathic generalized epilepsy not otherwise defined. The 182 residual children had cryptogenic (86) or symptomatic (67) partial epilepsy, and symptomatic or cryptogenic generalized epilepsy (29). Multivariate analysis of the 153 children with symptomatic or cryptogenic partial epilepsy retained sex, age, family history, postictal signs, 3-month remission during and terminal remission at 6 months in the model. Only the determinant ‘postictal signs’ was significant. After bootstrapping, the following results were found: the best cut-off value for P with

the highest sensitivity (0.65) and specificity (0.67) is at 0.39. The predictive value for TR5 <1 year for any value above this cut-off is 0.53 and the predictive value for TR5 >1 year for any value below the cut-off is 0.78. This amounts to 19 + 32 = 51 misclassifications (33%).

**Table 3.2B: Simple formula for the calculation of the prognosis with the above models**

| | Model with intake variables only | Model with intake and 6-month variables |
|---|---|---|
| If female, add | -37 | -45 |
| If age at intake > 6 years, add | 45 | 13 |
| If epileptiform features on first EEG, add | -28 | |
| If non-idiopathic etiology, add | -123 | -115 |
| If history of febrile seizures, add | -139 | -150 |
| If postictal signs present, add | -57 | -72 |
| If >25 seizures in first 6 months of follow-up, add | | 24 |
| If ≥3 months remission in first 6 months, add | | 49 |
| If TR at 6 months 2-6 months, add | | -41 |
| If TR at 6 months 0-2 months, add | | -135 |
| If combination of non-idiopathic etiology and history of febrile seizures, add | 166 | 167 |
| Constant x 100 | 228 | 256 |
| Calculate sum score of individual child | | |
| Cut-off value sum score | 110 | 132 |
| Good outcome predicted | Sum score > 110 | Sum score > 132 |
| Poor outcome predicted | Sum score < 110 | Sum score < 132 |

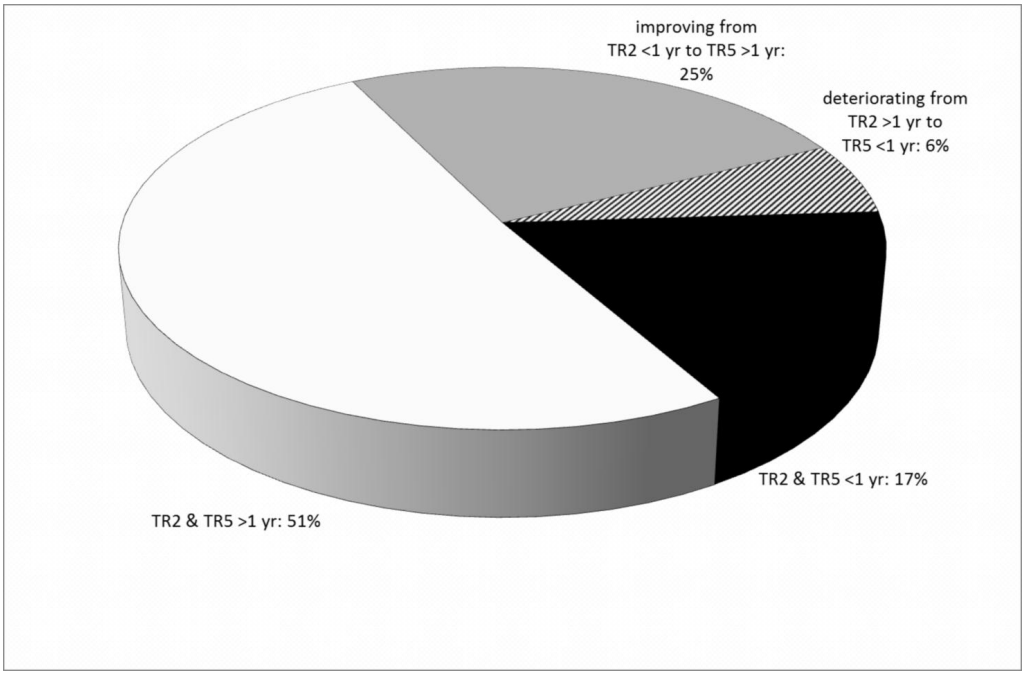
The numbers in the table are the RCs of each contributing variable multiplied by (-100) and the shrinkage factor. For the model based on intake variables only, the shrinkage factor derived from bootstrapping was 0.94 and for the model with intake and 6-month variables combined it was 0.90. For each variable, enter the number given in the table if the child has the defined category or property, but 0 if the child does not. For example, for a girl, enter 37 in the model with intake variables only and 45 in the model with intake and 6-month variables, but for a boy enter 0. The value for the interaction term can only be entered if both terms (non-idiopathic etiology and history of febrile seizures) are present. Adding the numbers for any particular child results in its sum score. This sum score has to be compared with the sum score cut-off value which was derived from the probability cut-off with the highest values for sensitivity and specificity. For the model with intake variables only, the cut-off was 110 and for the model with intake and 6-months variables it was 132. Values below the cut-off indicate a higher probability of TR5 <1 year and values above the cut-off indicate a smaller probability.

**Comparison of the results at 2 and at 5 years**

The correlation of the outcomes 2 and 5 years after intake, measured as continuous variables, was highly significant. For the 442 children whose outcome could be measured this way both at 2 and at 5 years, Kendall's tau-b correlation coefficient was 0.591 ($P < 0.0001$).

The correlation between the categorical remissions at 5 and 2 years is presented in **Figure 3.4**. In two children, the outcome at 2 and at 5 years could not be compared.

**Figure 3.4: Correlation between the categorical outcomes at 2 and 5 years for 453 children in the 5-year analysis. The outcome measures are terminal remission <1 year or >1 year at 2 and 5 years of follow-up**




TR5 was >1 year in 231 of the 259 children with a TR2 of >1 year (89%, or 51% of the entire cohort). In univariate analyses, this was associated with seizure type (absences and tonic–clonic seizures), epilepsy type (idiopathic generalized epilepsy), etiology (idiopathic), EEG (normal), remission of 3 months in the first 6 months of follow-up and absence of postictal signs, pre-existing neurological signs and imaging abnormalities. A deteriorating course was seen in 28 of the 259 children (11%, or 6% of the entire cohort). All of these had a TR2 of >1 but seizures during the fifth year. Significantly associated with a deteriorating course were age at onset >4 and the presence of postictal signs.

On the other hand, an improving course was seen in 113 out of 193 children with TR2 less than one year (59%, or 25% of the entire cohort) but TR5 >1 year. Six of these had been intractable at 2 years. An improving course was associated with seizure type (simple partial seizures), negative family history and abnormalities in imaging studies. A constantly poor course was observed in 78 children (17%) who attained a 1-year terminal remission neither at two nor at 5 years. Age at onset (<6 years), a large number of seizures before and in the 6 months after intake, seizure type (complex partial seizures, infantile spasms and myoclonic and atonic seizures), epilepsy type (symptomatic partial and cryptogenic partial and generalized), etiology (non-idiopathic), a history of febrile seizures and absence of remission during the first 6 months of follow-up were all associated with a constantly poor course.

Fifteen out of the 27 children who were intractable at 5 years had also been intractable at 2 years. Some other intractable children had had at least one long-term remission during the 5-year follow-up, but relapsed (**Table 3.3**). Two of these had had a remission of >2 years. More than half of the 108 children having seizures during the fifth year had had an intercurrent remission of at least 1 year.

**Table 3.3: Longest remission ever during 5 years of follow-up of 27 children matching the definition of intractable at 5 years, of 108 children with TR5 <1 year and of the remaining children with a TR5 of >1 year**

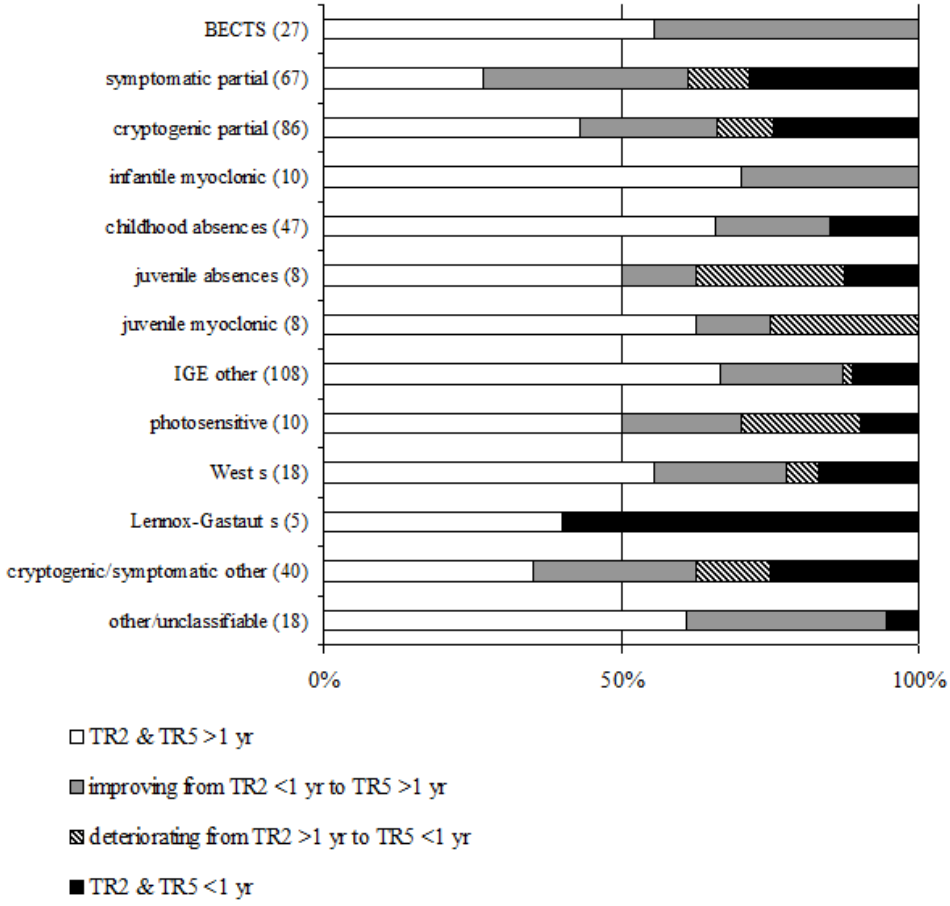
| | Number of children (%) | | |
|---|---|---|---|
| Longest remission during 5 years | 27 intractable children | 108 children with TR5 < 1 year | 345 children with TR5 ≥ 1 year |
| 0 – 3 months | 11 (41) | 13 (12) | 0 |
| 3 – 6 months | 6 (22) | 9 (8) | 0 |
| 6 – 12 months | 3 (11) | 19 (18) | 0 |
| 12 – 24 months | 5 (19) | 30 (28) | 29 (8) |
| > 24 months | 2 (8) | 37 (34) | 316 (92) |

**Results at the level of epileptic syndromes**

For virtually every syndrome, the largest group did well from the onset, and the second largest group showed an outcome improvement at 5 compared with 2 years (**Figure 3.5**). This was most obvious for benign partial epilepsy with rolandic spikes and for idiopathic generalized epilepsies. Much smaller groups of children doing poorly from the onset or showing a worse outcome at five than at 2 years were found mainly in the categories of symptomatic or cryptogenic epilepsies. Since the epileptic syndromes were classified in retrospect 2 years after the intake, syndromes were not included as a variable in the multivariate analyses. In the model with intake variables only, age

(<6 versus >6 years or older) was significant. Epileptic syndromes occurring at certain ages may have caused this. Therefore, we looked at the relation between age and outcome. In univariate analysis, age >6 years was associated with a significantly better outcome [odds ratio (OR) 0.46 with 95% confidence interval (CI) 0.23–0.92].

**Figure 3.5: Outcome at 2 and 5 years of 453 children followed for 5 years, according to epileptic syndrome (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) as defined 2 years after intake.**




Numbers in parentheses are numbers of patients.
BECTS: benign partial epilepsy of childhood with centrotemporal (rolandic) spikes,
IGE: idiopathic generalized epilepsy.

Stratifying for epilepsy syndrome did not yield a significant association between age and outcome [Mantel–Haenszel common odds ratio estimate: 0.71 (asymptotically 95% CI, 0.44, 1.14)], with one exception: age at intake <6 years had a worse prognosis if the child had symptomatic partial

epilepsy. Stratifying for age according to the five groups shown in **Table 3.1** demonstrated also that symptomatic partial had a worse outcome below the age of 6 years (significantly so between 3 and 6 years), whereas cryptogenic partial had a significantly worse outcome between 3 and 9 years. Idiopathic generalized syndromes had a better outcome in the younger age groups (significant at the ages of 3–9 years). Without exception, all idiopathic partial syndromes (mostly occurring between 6 and 12 years) had a good outcome. Our finding that age at intake was significant in the model with intake variables only may have been caused by the occurrence of epileptic syndromes at the various ages.

## DISCUSSION

The data presented here provide some insight in the evolution of childhood epilepsy over the years and in the variables that may influence the outcome. We hypothesized that we would be able to predict the outcome of childhood epilepsy based on (combinations of) determinants that can be identified at the moment of the diagnosis of epilepsy or shortly thereafter. Such a strategy might lead to individualized treatment regimens depending on the prognosis of the child. Evaluating this possibility, we were able to elaborate on the concept of 'smooth sailing epilepsy' (Camfield et al., 1990) on the one hand and of intractability (Huttenlocher and Hapke, 1990; Berg et al., 2001) on the other.

### Outcome and response to treatment

There seems to be a general consensus that both adults and children with newly diagnosed epilepsy have a 65–75% chance of entering long-term remission (Annegers et al., 1979; Beghi and Tognoni, 1988; Camfield et al., 1993; Cockerell et al., 1997, Sillanpää et al., 1998). About 10–15% are due to become really intractable and 10–25% end up somewhere in between. This is rather surprising in view of the large discrepancies in patient selection, duration of follow-up and outcome definitions in the cohorts described so far. In our cohort, we find a large proportion with an improving course over time whereas the proportion with a deteriorating course is relatively small. Eventually, the outcome figures resemble the general beliefs. Our data clearly show that this is a dynamic process, and that outcome is more dependent on the duration of follow-up than may previously have been thought.

The response to treatment with AEDs follows a pattern that bears superficial resemblance to the one that has recently been described in the retrospective study by Kwan and Brodie (2000) in a hospital-based patient group aged 9 to 93 years, but our final results are better. They found a success rate

(seizure free for at least 1 year at the time of last follow-up) for the first AED in 47% of all patients treated, for the second in 13%, and in 4% for any further AED regime. They do not state the number of patients who were not treated. In our childhood cohort, the 388 treated children have similar results: 46% had a TR5 >1 year on the first AED, 19% on the second and 9% on any further AED regime. However, the success rate of any further AED or AED combination after the first AED had failed was almost twice as high (58%; Kwan and Brodie, 32%). The better results found by us and by Camfield et al. (1993) were probably largely caused by the different composition of the groups investigated: children versus all ages, and (largely) population-based versus hospital-based. Therefore, we want to stress that, at least in children, failure of one (or two) AED(s) certainly is a risk factor for a poor outcome, but that a considerable proportion of these patients will do well in the end.

**Course during the follow-up**

In more than two-thirds of patients, the 5-year outcome mirrored the 2-year outcome (in 51% both >1 year, in 17% both <1 year). For the best seizure–outcome group, the relevant variables pointed heavily to all qualities of 'idiopathic' as the main predictor. For the worst outcome group, indications for a symptomatic or cryptogenic etiology and for malignant types of seizures or epilepsy, an early age at onset and a history of febrile seizures (despite the absence of children with severe myoclonic epilepsy of childhood in our cohort) were the leading variables.

An improving course was seen in one quarter of the cohort. The association of the improvement with simple partial seizures may be partly explained by the presence of a considerable number of children with benign partial epilepsy in this group. In this clinical epidemiological study, their long-term outcome was invariably good (**Figure 3.5**), in contrast to the outcome at 2 years. This finding is in agreement with a recent meta-analysis of studies on benign partial epilepsy of childhood with rolandic spikes (Bouma et al., 1997). But the number of children with a remote symptomatic etiology, who attained a TR5 of >1 year, also increased by almost 25% in comparison with TR2 (**Table 3.1**). Deterioration after a favorable early course was much less frequent (6% of our entire cohort) than improvement after an initially poor course. This was associated with the variable age at onset above 9 years.

Our data suggest that the two main outcome groups at 5 years (the first 'good to excellent', the second 'poor') predominate numerically and that the in-between group is relatively small (**Figure 3.1**). After a longer follow-up, the outcomes become better more often than worse for children who do not have a stable course of their epilepsy. The improvement found in about one-quarter of the children adds to the good result of the children with smooth-sailing epilepsy. On the other hand, the number of children found to be intractable had not decreased when we compared the outcome at 2

and 5 years. Children who deteriorated took the place of children who had improved. Further follow-up is mandatory to find out whether the intractability leading to an indication for epilepsy surgery at adult age may arise after a (much) longer delay (Berg et al., 2003).

**Intractability**

Our finding that the number of children with a worsening course was relatively small confirms our idea that childhood epilepsy is generally not a progressive disease (van Donselaar et al., 1997). This is in contrast to the opinion of those authors adhering to Gowers' dictum that 'seizures beget seizures' (Gowers, 1881; Reynolds et al., 1983). However, fluctuations during the course do occur and even fulfilling criteria for intractability may be a temporary phenomenon. Of the 419 patients with a seizure-free period of at least 12 months at any time during the follow-up, 74 (18%) did not reach a TR5 of >1 year and seven (2%) became intractable (**Table 3.3**). On the other hand, 10 of the 25 children considered intractable at 2 years were not intractable at 5 years and six even had a TR5 of >1 year. In the Connecticut study (Berg et al., 2001), there was no fixed duration of follow-up but the range and median duration of follow-up were given. Intractability was considered to be early if it began within the first 2 years of follow-up and was observed during at least 18 months. Ten per cent of the children fulfilled their criteria for early intractability, comparable to our findings (6%). Of their 60 children with early intractability, seven (12%) went on to attain a remission of at least 1 year. In our cohort, this was 24% (six out of 25 children). Other authors found that in a group of children that had been refractory to AED therapy for at least 2 years, about 4% entered remission during each year of further follow-up (Huttenlocher and Hapke, 1990). A recent editorial comment (Holmes and Engel, 2001), therefore, rightly cautions against an early rush to aggressive intervention, but on the other hand acknowledges the possibly adverse effects of a period with continuing seizures, fitting the definition of at least temporary intractability, on the patient and his or her family. Improvement in the course of lesional epilepsy in childhood may come late, and our findings clearly underscore the need for a careful decision about which children should be referred for epilepsy surgery and when. It is difficult to give an accurate and broad definition of medical intractability. Not being in remission is insufficient, since treatment, duration of remission, number and/or frequency of seizures and the time interval during which seizures were counted should be specified. To predict intractability correctly, there should not be too many false-negatives and false-positives. It would be worthwhile to develop a consensus on the definition or definitions of intractability, enabling investigators to compare the results of various studies. The definitions applied in this study were used in various publications by Berg and colleagues and also in our former study on the 2-year outcome of childhood epilepsy.

**Smooth course**

A considerable proportion of our cohort fulfilled one or more criteria for an uncomplicated course. Sixty-five (14%) children were completely seizure free since the intake (28 without treatment, 35 successfully withdrawn from AEDs), and 122 (27%) came into terminal remission during the first year of follow-up (17 without treatment, 95 successfully withdrawn). For such a favorable course, Camfield and colleagues coined the term 'smooth-sailing epilepsy' (Camfield et al., 1990). By this, they meant the children who became seizure free immediately after the start of AED treatment and remained seizure free during the follow-up, even after the withdrawal of medication. In their cohort (Camfield et al., 1993), this group comprised 20% of the entire sample. To this could be added a group that had never been treated at all (3%). It can be concluded from their and our data that smooth-sailing epilepsy does exist and accounts for at least a quarter—more probably a third or more—of all children with newly diagnosed epilepsy.

**Determinants, outcome prediction**

Both in the univariate and in the multivariate analysis, the variables reaching significance in the prediction of the outcome were largely identical at 5 years compared with 2 years of follow-up. The modelling strategy used in the present analysis, including interaction terms, seems to predict the outcome better than the variables per se. Notably, we found a dichotomy concerning etiology. In the group with idiopathic etiology, febrile seizures were a significant predictor of a worse outcome. In the group with non-idiopathic etiology, this predictor was no longer significant. As far as we know, this has not been reported before.

Variables predictive of the outcome of childhood epilepsy in multivariate analyses were found to be etiology, seizure type, early response to treatment (Sillanpää et al., 1998), number of pretreatment seizures, age at onset and a history of neonatal convulsions (Camfield et al., 1993). In these and our studies, children with clear mental retardation were considered to have remote symptomatic epilepsy. Except for age at onset and history of neonatal convulsions (which was not recorded by us), our findings were similar. Camfield and colleagues found age at onset below 12 years to be predictive of remission. Our group of patients older than 12 years was perhaps too small to confirm this finding. In our cohort, secondary deterioration was associated with age at intake above 9 years. Otherwise, the influence of age seemed to be correlated with epilepsy syndromes and the age at which they usually occur.

A model with determinants identified at intake was able to predict the outcome at 5 years correctly in 64% of our cohort. With the model based on the intake and 6-month variables together, the outcome was correctly classified in 70% of the cohort. In our earlier study, the outcome at 2 years of follow-up was predicted correctly in 70 and 76% (Arts et al., 1999). These data suggest that

predictive models have a place in the determination of the prognosis of childhood epilepsy, especially in the prediction of a long terminal remission. When the models predict a long terminal remission, the chance that the prediction will be incorrect is much smaller than when they predict a short terminal remission. The resulting expectations may be used to inform the parents, and as a basis for the choice of treatment strategy. Caution with the interpretation of such predictions is warranted, however, because the number of those misclassified (especially children predicted to have a poor outcome) is considerable due to the lack of sensitivity of the models. Nevertheless, it is justified to ask whether AED treatment really would be necessary if the prognosis is good, and whether early aggressive intervention could prevent the development of expected intractability. Our findings indicate that there are no ethical or practical objections against designing studies that aim to test hypotheses based upon these questions.

## ACKNOWLEDGEMENTS

The authors wish to thank Anne Berg for her valuable comments and Wiebe Pestman for his help with the bootstrap techniques. Secretarial assistance was provided by Mrs A. Westendorp, S. Lohman and M. Bakker. The Dutch National Epilepsy Fund (grants A72 and A86) and the JANIVO fund supported the study financially.

## REFERENCES

Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979; 20: 729–37.

Arts WF, Geerts AT, Brouwer OF, Boudewijn Peters AC, Stroink H, van Donselaar CA. The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood. Epilepsia 1999; 40: 726–34.

Beghi E, Tognoni G. Prognosis of epilepsy in newly referred patients: a multicenter prospective study. Epilepsia 1988; 29: 236–43.

Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. Neurology 2001; 56: 1445–52.

Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, et al. How long does it take for partial epilepsy to become intractable? Neurology 2003; 60: 186–90.

Bouma PA, Bovenkerk AC, Westendorp RG, Brouwer OF. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. Neurology 1997; 48: 430–7.

Callenbach PM, Westendorp RG, Geerts AT, Arts WF, Peeters EA, van Donselaar CA, et al. Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood. Pediatrics 2001; 107: 1259–63.

Camfield CS, Camfield PR, Gordon KE, Dooley JM. A population-based study of epilepsy that does not recur on treatment and remits when medication is stopped: smooth-sailing epilepsy. Ann Neurol 1990; 28: 471–2.

Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. J Pediatr 1993; 122: 861–8.

Cockerell OC, Johnson AL, Sander JWAS, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. Epilepsia 1997; 38: 31–46.

Commission on Epidemiology and Prognosis of the International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Epilepsia 1993; 34: 592–6.

Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30: 89–99.

Gowers WR. Epilepsy and other chronic convulsive disorders. London: Churchill; 1881.

Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996; 15: 361–87.

Hirtz D, Berg A, Bettis D, Camfield C, Camfield P, Crumrine P, et al. Practice parameter: treatment of the child with a first unprovoked seizure. Neurology 2003; 60: 166–75.

Holmes GL, Engel J Jr. Predicting medical intractability of epilepsy in children: how certain can we be? Neurology 2001; 56: 1430–1.

Huttenlocher PR, Hapke RJ. A follow-up study of intractable seizures in childhood. Ann Neurol 1990; 28: 699–705.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000; 342: 314–9.

Peters AC, Brouwer OF, Geerts AT, Arts WF, Stroink H, van Donselaar CA. Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy. Neurology 1998; 50: 724–30.

Reynolds EH, Elwes RDC, Shorvon SD. Why does epilepsy become intractable? Lancet 1983; 2: 952–4.

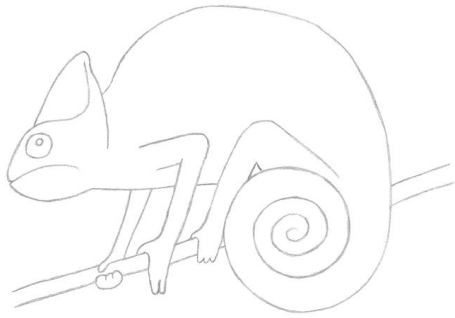
Shinnar S, Berg AT. Does antiepileptic drug therapy prevent the development of ‘chronic’ epilepsy? Epilepsia 1996; 37: 701–8.

Shorvon SD. The temporal aspects of prognosis in epilepsy. J Neurol Neurosurg Psychiatry 1984; 47: 1157–65.

Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. N Engl J Med 1998; 338: 1715–22.

van Donselaar CA, Brouwer OF, Geerts AT, Arts WFM, Stroink H, Peters ACB. Clinical course of untreated tonic-clonic seizures in childhood: prospective, hospital based study. BMJ 1997; 314: 401–4.

# Chapter 4 Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood



Ada T. Geerts, Willem Frans M. Arts, Hans Stroink, Els A.J. Peeters, Oebele F. Brouwer, A.C. Boudewijn Peters, Laura A.E.M. Laan, and Cees A. van Donselaar

*Epilepsia (2010),* ***51*** *(7), 1189-1197*

**ABSTRACT**

The purpose was to study the course and outcome of childhood-onset epilepsy during 15-year follow-up (FU). We extended FU in 413 of 494 children with new-onset epilepsy recruited in a previously described prospective hospital-based study by questionnaire.

Mean FU was 14.8 years (range 11.6–17.5 years). Five-year terminal remission (TR) was reached by 71% of the cohort. Course during FU was favorable in 50%, improving in 29%, and poor or deteriorating in 16%. Mean duration of seizure activity was 6.0 years (range 0–21.5 years), strongly depending on etiology and epilepsy type. Duration was <1 year in 25% of the cohort and exceeded 12 years in another 25%. Antiepileptic drugs (AEDs) were used by 86% during a mean of 7.4 years: one-third had their last seizure within 1 year of treatment, and one third continued treatment at the end, although some had a 5-year TR. At last contact, 9% of the cohort was intractable.

In multivariate analysis, predictors were non-idiopathic etiology, febrile seizures, no 3-month remission, and early intractability. Eighteen patients died; 17 had remote symptomatic etiology. Standardized mortality ratio for remote symptomatic etiology was 31.6 [95% confidence interval (CI) 18.4–50.6], versus 0.8 [95% CI 0.02–4.2] for idiopathic/cryptogenic etiology.

In most children with newly diagnosed epilepsy, the long-term prognosis of epilepsy is favorable, and in particular, patients with idiopathic etiology will eventually reach remission. In contrast, epilepsy remains active in ~30% and becomes intractable in ~10%. AEDs probably do not influence epilepsy course; they merely suppress seizures. Mortality is significantly higher only in those with remote symptomatic etiology.

**INTRODUCTION**

Knowledge of the long-term outcome of epilepsy is of the utmost importance in the treatment of children with epilepsy. Many investigators have studied cohorts with the purpose of describing epidemiology, prognosis, and mortality, as well as social and educational outcomes (Camfield et al., 1993; Berg et al., 1999b; Wakamoto et al., 2000; Sillanpää & Schmidt, 2009). Next to methodology and cohort size, length of follow-up (FU) determines the significance of the results of these studies, especially when it comes to aspects such as course of epilepsy, intractability, terminal remission, and mortality. A lifelong FU of cohorts would be ideal to cover all aspects; however, although this has not yet been realized, studies with prolonged FU are valuable.

Whereas outcome in terms of remission or death can be determined easily, the course of epilepsy during FU is more difficult to describe. This can be done in terms of success or failure of antiepileptic drugs (AEDs), or in terms of remission and relapse (Camfield et al., 1993; Sillanpaa &

Schmidt, 2006). The course of epilepsy is in our view important to investigate, because intra- and inter-individual variation may be considerable (Berg et al., 2006; Sillanpää & Schmidt, 2006). Periods of remission and relapse may interchange. Such a dynamic course might influence our interpretation of the results of prognostic studies, advice to patients, treatment strategies, and timing of referral for surgery. Moreover, it is still largely unknown whether the long-term outcome of epilepsy is determined by its natural course or whether it can be modified by treatment. Long-term FU studies may be helpful to solve this dispute.

Between 1988 and 1992 we consecutively recruited children who attended hospital with new-onset epilepsy. Results at 2 and 5 years after diagnosis have already been published (Arts et al., 1999, 2004). We extended the FU of 413 children to a mean of 15 years. To date, there have been no reports of studies with cohorts of this size combined with this length of FU. The main purpose of this study was to investigate course and outcome of childhood epilepsy and its determinants, treatment, and mortality.

## METHODS

### Setting

Between 1988 and 1992, we recruited a hospital-based cohort (n = 494) of children aged 1 month to 16 years with newly diagnosed epilepsy. The original 2-year FU was prolonged to 5 years. About 10 years later, we contacted the cohort again. Four hospitals in The Netherlands participated in this study. Written informed consent was given by all parents and children of 12 years or older, not intellectually handicapped. The hospitals ethical committees approved the study.

### Cohort

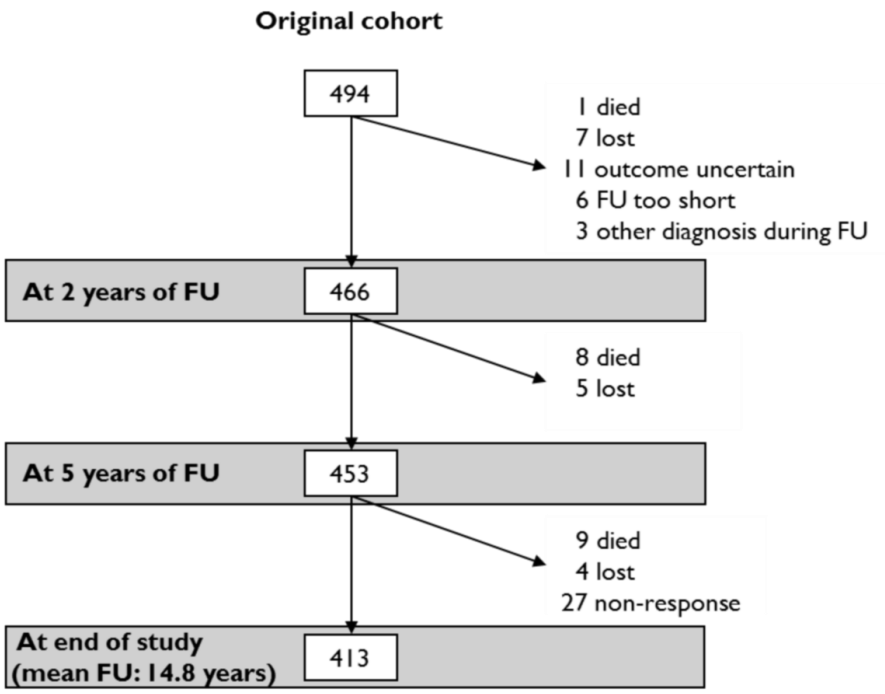
All 494 children experienced at least two unprovoked— not acute symptomatic—epileptic seizures or one unprovoked status epilepticus (SE) before enrollment. Subjects with SE have been described in detail (Stroink et al., 2007). The 453 subjects with a 5-year FU were the starting point of this study (**Figure 4.1**). Detailed descriptions of the original study and the results at 2 and 5 years of FU have been published (Arts et al., 1999, 2004; Callenbach et al., 2001). The recruitment rate of the original study approximated 75% of the expected annual incidence in the referral area (Arts et al., 1999).

### Classifications

A panel of three pediatric neurologists classified the seizures and epilepsies shortly after enrollment (Gastaut, 1969; ILAE, 1981). At 2 years of FU, the original classifications were replaced by the

later classifications of the International League against Epilepsy (ILAE, 1989). Etiology was idiopathic, cryptogenic, or remote symptomatic, including mental retardation (ILAE, 1993). Children were mentally retarded if specialized care or schooling for the intellectually disabled was needed (presumed IQ <70) (Hauser et al., 1982).

**Figure 4.1: Diagram of the cohort. FU, follow-up**




**Follow-up and questionnaire**

During the first 5 years of FU, children attended hospital at regular intervals. After 5 years, the regular check-ups stopped according to the study protocol. Between 2004 and 2006, all subjects or their parents received a questionnaire with items concerning their epilepsy. A total of 453 questionnaires were sent of which we received 413 in return. Five subjects had emigrated, eight had died, two subjects refused to cooperate and returned their forms uncompleted, and 25 did not respond despite reminders. The response rate based on the original 494 subjects was 84%.

**Definitions**

Terminal remission ($TR_E$) was defined as the interval between the last seizure and the end of FU. Intractability: no remission exceeding 3 months during a 1-year period of observation despite

adequate treatment during that year and the years before (Arts et al., 2004). In this study, adequate treatment was considered to be the optimal use of at least two AEDs, either alone or in combination. Active epilepsy: at least one seizure in the last 5 years of FU, regardless of actual or earlier treatment (ILAE, 1993). Fast response to AED: starting a 6-month remission within 2 months after starting treatment.

We assessed the course of epilepsy by comparing the second year, the fifth year, and the last year of FU on the occurrence of seizures or not. Course was favorable if all 3 years were without seizures; improving with seizures in the second year, but remission in the last year regardless of the outcome of the fifth year; poor with seizures in all 3 years; deteriorating with remission in the second year, but with seizures in the last year regardless of the outcome in the fifth year; and varying with outcome in the fifth year opposite to outcome in both other years.

We considered the interval between the very first seizure in life and the last seizure before last contact as duration of seizure activity. Possible sudden unexpected death in epilepsy (SUDEP) includes cases in which SUDEP cannot be ruled out but there is insufficient evidence regarding the circumstances of death and no postmortem report is available (Annegers & Coan, 1999).

**Statistical analysis**

Data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, U.S.A.). We assessed the standardized mortality ratio (SMR) to evaluate the risk of dying in our cohort compared with the general Dutch population in 2004. We used binary logistic regression to study the strongest predictors of intractability (stepwise backward conditional method). The area under the receiver operating characteristic (ROC) curve was used as a measure of accuracy. An area of 1 represents a perfect test and an area of 0.5 represents a worthless test. We used one-way analysis of variance (ANOVA) to compare means, and Pearson chi-square or likelihood-ratio square to compare proportions.

**RESULTS**

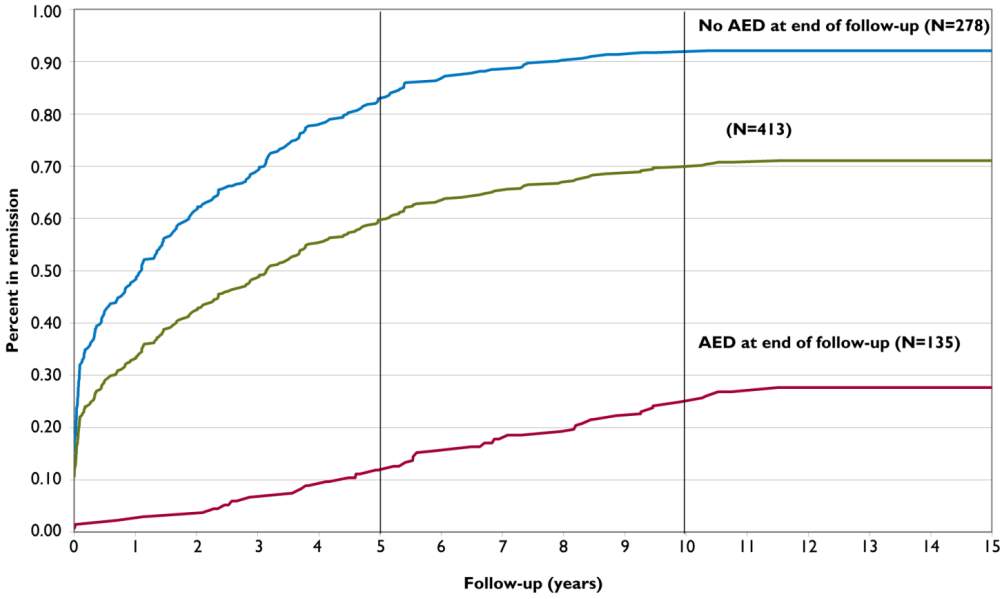
A total of 413 subjects were analyzed, of whom 47% were male. The mean age at onset of epilepsy was 5.5 years (median 5.1; range 1 month to 15.5 years), and the mean age at last contact was 20.8 years (median 20.4; range 12.2–32.5 years). Etiology was idiopathic in 50.8%, remote symptomatic in 27.8%, and cryptogenic in 21.3%. The mean FU was 14.8 years (median 14.8; range 11.6–17.5 years).

**Final outcome**

Two hundred ninety-three subjects had a $TR_E$ of at least 5 years at the end of the study (70.9%: 61.9% off AEDs, 9.0% on AEDs). **Figure 4.2** shows the proportion of subjects reaching their 5-year $TR_E$ during the years of FU. It demonstrates for example that at 5 years after enrollment 60% of the cohort reached their $TR_E$. An extra **Figure S1** showing the proportion of subjects reaching a 2-year $TR_E$ may be found in **Appendix 3**.

In addition to the 293 subjects in remission, epilepsy was still active in the remaining 120 subjects (29.1%: 5.3% off AEDs, 23.7% on AEDs). Thirty-five subjects were intractable in the final year of FU, with no remissions exceeding 3 months despite adequate treatment (8.5%). **Table 4.1** shows the proportion of subjects in remission or with intractability for each epilepsy type and syndrome.

**Figure 4.2: Cumulative proportion reaching a 5-year terminal remission ($TR_E$) during follow-up. AED, antiepileptic drug.**




**Course during FU**

A favorable course was found in 48.4% of all subjects, with no seizures in the second, fifth, and final year of FU. The next largest was the group with an improving course (29.1%), with seizures in the second year, but with remission in the fifth year or later. Furthermore, 9.9% had a poor course with seizures in each of the 3 years, 6.1% had a deteriorating course, whereas a varying course was found in 6.5%. The age at onset was significantly different between the groups (**Table 4.2**).

**Table 4.1: Remission, intractability, course of epilepsy, and seizure activity during follow-up for each epilepsy type and syndrome (ILAE)**

| | N | Remission (%) | Intractable (%) | Favorable course (%) | Improving course (%) | Varying course (%) | Deteriorating course (%) | Poor course (%) | Interval first and last seizure in years median (range) |
|---|---|---|---|---|---|---|---|---|---|
| Benign childhood epilepsy with centro-temp spikes | 23 | 100.0 | 0 | 60.9 | 39.1 | 0 | 0 | 0 | 1.2 (0.0-13.1) |
| Localization-related symptomatic | 59 | 54.2 | 13.6 | 18.6 | 40.7 | 13.6 | 13.6 | 13.6 | 8.3 (0.0-16.7) |
| Localization-related cryptogenic | 78 | 66.7 | 12.8 | 37.2 | 34.6 | 3.8 | 6.4 | 17.9 | 4.3 (0.0-21.5) |
| Benign myoclonic epilepsy in infancy | 9 | 100.0 | 0 | 77.8 | 22.2 | 0 | 0 | 0 | 0.8 (0.2-8.5) |
| Childhood absence epilepsy | 45 | 82.2 | 2.2 | 68.9 | 22.2 | 4.4 | 0 | 4.4 | 2.2 (0.2-15.3) |
| Juvenile absence epilepsy | 8 | 75.0 | 12.5 | 50.0 | 12.5 | 12.5 | 12.5 | 12.5 | 1.9 (0.2-17.6) |
| Juvenile myoclonic epilepsy | 7 | 57.1 | 0 | 57.1 | 0 | 28.6 | 14.3 | 0 | 3.3 (0.8-16.1) |
| Generalized idiopathic epilepsy on awakening | 6 | 50.0 | 0 | 16.7 | 0 | 33.3 | 33.3 | 16.7 | 8.6 (1.0-14.5) |
| Generalized idiopathic epilepsy other | 91 | 76.9 | 3.3 | 62.6 | 25.3 | 2.2 | 3.3 | 6.6 | 2.6 (0.0-20.2) |
| Generalized idiopathic epilepsy precipitated | 10 | 60.0 | 0 | 50.0 | 40.0 | 0 | 0 | 10.0 | 5.6 (0.0-16.7) |
| West syndrome | 19 | 57.9 | 21.1 | 52.6 | 21.1 | 10.5 | 5.3 | 10.5 | 5.1 (0.1-15.6) |
| Lennox-Gastaut syndrome | 5 | 0 | 80.0 | 0 | 0 | 0 | 40.0 | 60.0 | 15.1 (12.2-16.2) |
| Myoclonic astatic epilepsy | 7 | 42.9 | 28.6 | 14.3 | 42.9 | 14.3 | 14.3 | 14.3 | 12.5 (0.8-16.9) |
| Myoclonic absence epilepsy | 1 | 100.0 | 0 | 0 | 100 | 0 | 0 | 0 | 5.1 |
| Other symptomatic generalized epilepsies | 20 | 75.0 | 5.0 | 50.0 | 30.0 | 15.0 | 0 | 5.0 | 6.4 (0.0-15.0) |
| Specific syndromes* | 9 | 66.7 | 11.1 | 33.3 | 33.3 | 11.1 | 11.1 | 11.1 | 7.7 (0.4-15.4) |
| Landau-Kleffner syndrome | 1 | 100.0 | 0 | 100.0 | 0 | 0 | 0 | 0 | 11.3 |
| Without unequivocal generalized or focal features | 1 | 100.0 | 0 | 100.0 | 0 | 0 | 0 | 0 | 0.3 |
| Status epilepticus | 4 | 100.0 | 0 | 100.0 | 0 | 0 | 0 | 0 | 0 |
| Unclear | 10 | 90.0 | 0 | 70.0 | 30.0 | 0 | 0 | 0 | 2.1 (0.1-13.3) |
| Total | 413 | 70.9 | 8.5 | 48.4 | 29.1 | 6.5 | 6.1 | 9.9 | 3.7 (0.0-21.5) |

* Angelman syndrome (5), Rett syndrome, tuberous sclerosis with normal intelligence, Down syndrome, trisomy 22.

**Table 4.2: Significant differences between groups with a different course of epilepsy during follow-up (FU)**

| | Favorable | Improving | Varying | Deteriorating | Poor |
|---|---|---|---|---|---|
| Number | 200 (48.4%) | 120 (29.1%) | 27 (6.5%) | 25 (6.1%) | 41 (9.9%) |
| Mean age at onset in years* (median; range) | 5.4 (5.1; 0-15.5) | 5.5 (5.3; 0-15.2) | 6.8 (6.2; 0.3-13.7) | 7.3 (8.0; 0.1-12.9) | 4.2 (2.6; 0-15.3) |
| Etiology** | | | | | |
| - idiopathic | 129 (64.5%) | 51 (42.5%) | 10 (37.0%) | 8 (32.0%) | 12 (29.3%) |
| - remote symptomatic | 36 (18.0%) | 40 (33.3%) | 14 (51.9%) | 12 (48.0%) | 13 (31.7%) |
| - cryptogenic | 35 (17.5%) | 29 (24.2%) | 3 (11.1%) | 5 (20.0%) | 16 (39.0%) |
| Fast response to AED** | | | | | |
| - no | 58 (29.0%) | 62 (51.7%) | 14 (51.9%) | 13 (52.0%) | 34 (82.9%) |
| - yes | 96 (48.0%) | 50 (41.7%) | 10 (37.0%) | 11 (44.0%) | 6 (14.6%) |
| - no AED | 46 (23.0%) | 8 (6.7%) | 3 (11.1%) | 1 (4.0%) | 1 (2.4%) |
| 3-month remission in first 6 months** | | | | | |
| - no | 33 (16.5%) | 45 (37.5%) | 6 (22.2%) | 2 (8.0%) | 26 (63.4%) |
| - yes | 167 (83.5%) | 75 (62.5%) | 21 (77.8%) | 23 (92.0%) | 15 (36.6%) |
| Mean $LR_5$ in years** (median; range) | 4.4 (4.9; 1.5-5.0) | 2.6 (2.8; 0.2-5.0) | 3.0 (3.1; 1.8-4.8) | 3.6 (3.4; 1.4-5.0) | 0.9 (0.7; 0-3.0) |
| Mean number of AEDs[1] ** (median; range) | 1.0 (1.0; 0-3) | 2.0 (2.0; 0-9) | 1.9 (1.0; 0-7) | 2.0 (2.0; 0-5) | 3.5 (3.0; 0-8) |

AED, antiepileptic drug.
[1] = mean number of AEDs during the first 5 years of FU, $LR_5$: longest remission during first 5 years of FU, *$p < 0.05$, **$p < 0.0001$.
Course was based on the occurrence of seizures or not in the second year, the fifth year, and the last year of FU.

In those with a favorable course idiopathic etiology was predominant, and the mean longest remission during the first 5 years of FU (LR5) was significantly higher than in all other groups. In contrast, the group with a poor course had the lowest LR5, only 36.6% had a 3-month remission in the first 6 months of FU, and only 14.6% had a fast AED response. There was no difference in time to treatment between the groups.

In the last year of FU, 63.4% of the poor group was intractable, whereas this was 28.0% in the deteriorating and 14.8% in the varying group. On the other hand, 93.0% of the favorable group had a $TR_E$ >5 years, 80.8% of the improving, and 37.0% of the varying group. **Table 4.1** shows the course for each epilepsy type and syndrome separately, which differed significantly between the groups ($p < 0.0001$).

**Early good course**

An early good course was found in 35% of our cohort: 144 subjects were completely free of seizures during the first 5 years of FU (n = 58) or had seizures during the first 6 months only and subsequently were in remission until 5 years after enrollment (n = 86). AEDs were prescribed in 112 subjects (77.8%). After these 5 years, 25 subjects relapsed (17.4%). For only 10 subjects, we found an explanation: five had photosensitivity, one had seizures due to an arteriovenous malformation diagnosed at enrollment, and four had epilepsy with a high relapse rate (West syndrome, Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, and generalized tonic–clonic seizures on awakening). Only three of the 25 subjects used AED at the time of relapse [photosensitivity (2), Rett syndrome]. One other subject with photosensitivity relapsed after AED withdrawal. All others had been without treatment for many years following their long remission, excluding withdrawal as a cause of relapse.

Fourteen of the 25 with a relapse ended with active epilepsy—most of the 10 subjects mentioned above for whom we found an explanation. Two of those with active epilepsy were intractable in the last year of FU (Lennox-Gastaut, symptomatic multifocal epilepsy).

Idiopathic etiology was more frequent in the group with an early good course than in the remainder of the cohort: 64.6% versus 43.5% [95% confidence interval (CI) of the difference: 11.8–31.3%]. Relapse was found in 38% of subjects with remote symptomatic etiology versus 13% of those with idiopathic and 8% of those with cryptogenic etiology.

**Duration of seizure activity**

The mean interval between the very first seizure in life and the last reported seizure during this study was 6.0 years (median 3.7; range 0.0–21.5 years). **Table 4.1** shows this duration of seizure

activity for each epilepsy type or syndrome. The mean intervals differed significantly ($p < 0.0001$). In 25% of the cohort, the interval was <1 year, and in another 25% of the cohort it was >12 years. Etiology strongly influenced the duration of seizure activity. Idiopathic etiology had a mean duration of 4.5 years (95% CI 3.8–5.3; median 2.3 years), whereas in remote symptomatic etiology it was 8.1 years (95% CI 7.0–9.2; median 7.6 years). Cryptogenic etiology had a mean duration of 6.6 years (95% CI 5.3–7.9; median 4.3 years). At 5 years after onset, 68.3% of the subjects with idiopathic etiology had their last seizure: 53.4% of those with cryptogenic and 39.5% of those with remote symptomatic etiology ($p < 0.0001$). At 10 years these numbers were 79.0% for idiopathic, 65.9% for cryptogenic and 55.3% for remote symptomatic etiology ($p < 0.0001$).

**Treatment**

During the entire FU, 356 of the 413 subjects started treatment (86.2%). For each etiological category, the mean number of years during which AEDs were used is shown in **Table 4.3**, uncorrected for periods without AEDs in-between. One-third of the subjects had their very last seizure within the first year of treatment.

Before the end of FU, 221 of the 356 subjects discontinued treatment (62.1%). Their mean number of treatment years was 3.2 years (median 2.0; range 0.1–14.8 years). Beside this group, 135 subjects (37.9%) continued treatment until the end of FU, 50 of them using polytherapy. Sixty-nine of these 135 (51.1%) had seizures in the last year of FU, and 37 (27.4%) were in remission for at least 5 years. Reasons for continuing AEDs were among others: photosensitivity (9), juvenile myoclonic epilepsy (2), fear of new seizures (4), failed trials of stopping treatment (4), and ‘‘infantile convulsions and choreoathetosis’’ (1). **Table 4.4** shows the AEDs used at the end of FU. At last contact, the 98 subjects with active epilepsy more often used new drugs available since 1993 (gabapentin, lamotrigine, topiramate, oxcarbazepine, and levetiracetam) than the 37 subjects in remission: 51.0% versus 18.9% (95% CI of difference 16.1–48.1%).

During the entire FU, 57 subjects never used AEDs (13.8% of 413). Their final outcome, with >90% in remission, was comparable with those stopping AED >5 years before the end of FU. These two groups did not differ in etiology and epilepsy type. However, subjects never using AEDs were younger at epilepsy onset (4.1 vs. 5.4 years; 95% CI of difference 0.2–2.4) and had fewer seizures before enrollment (<25 seizures before enrollment: 78.9% vs. 58.7%; 95% CI of difference 7.7–32.7).

**Table 4.3: AED treatment and its outcome for each etiological category separately**

| | Etiology | Mean number of years of AED use (median, range) | AED use at 5 years after start of AED | Last seizure within 1st year of AED use | Remission ($TR_E$ > 5yrs) | Intractable in final year |
|---|---|---|---|---|---|---|
| All subjects who started treatment | Idiopathic: 172 (48.3%) | 5.7 (3.1; 0.1-16.8)* | 61 (35.5%)# | 76 (44.2%)# | 133 (77.3%)# | 6 (3.5%)# |
| | Remote sympt.: 108 (30.3%) | 9.8 (12.9; 0.5-16.8) | 76 (70.4%) | 18 (16.7%) | 60 (55.6%) | 17 (15.7%) |
| | Cryptogenic: 76 (21.3%) | 8.1 (7.5; 0.1-16.4) | 45 (59.2%) | 18 (23.7%) | 47 (61.8%) | 12 (15.8%) |
| | Total: 356 (100.0%) | 7.4 (5.2; 0.1–16.8) | 182 (51.1%) | 112 (31.5%) | 240 (67.4%) | 35 (9.8%) |
| Subjects who discontinued AED before final contact | Idiopathic: 127 (57.5%) | 2.7 (1.2; 0.1-14.2)* | 16 (12.6%)# | 73 (57.5%)* | 121 (95.3%)* | 0 |
| | Remote sympt.: 50 (22.6%) | 4.1 (3.6; 0.5-14.8) | 18 (36.0%) | 17 (34.0%) | 41 (82.0%) | 0 |
| | Cryptogenic: 44 (19.9%) | 3.5 (2.4; 0.1-13.0) | 13 (29.5%) | 18 (40.9%) | 41 (93.2%) | 0 |
| | Total: 221 (100.0%) | 3.2 (2.0; 0.1–14.8) | 47 (21.3%) | 108 (48.9%) | 203 (91.9%) | 0 |

AED, antiepileptic drug.

* Idiopathic etiology significantly differed from remote symptomatic etiology ($p < 0.05$).

\# Idiopathic etiology significantly differed from remote symptomatic etiology as well as from cryptogenic etiology ($p < 0.05$).

**Table 4.4: AEDs used at the end of follow-up**

| | Freq | | Freq |
|---|---|---|---|
| valproic acid | 76 | ethosuximide | 5 |
| carbamazepine | 38 | topiramate | 4 |
| lamotrigine | 28 | phenytoin | 3 |
| oxcarbazepine | 17 | phenobarbitone | 1 |
| clobazam | 12 | vigabatrin | 1 |
| levetiracetam | 12 | gabapentin | 1 |
| clonazepam | 6 | oxazepam | 1 |

AED, antiepileptic drug.

**Table 4.5: Results from the multivariate logistic regression analysis predicting intractability at the end of follow-up (stepwise backward, conditional)**

| | Wald statistic | Degrees of freedom | p-Value | Odds Ratio (95% CI) |
|---|---|---|---|---|
| Etiology | 7.20 | 2 | .027 | |
| - Remote symptomatic versus idiopathic | 5.24 | 1 | .022 | 3.59 (1.20; 10.72) |
| - Cryptogenic versus idiopathic | 6.48 | 1 | .011 | 4.44 (1.41; 14.00) |
| History of febrile seizures | 3.37 | 1 | .067 | 2.80 (0.93; 8.42) |
| 3-Month remission in first 6 months of FU | 3.12 | 1 | .077 | 0.44 (0.18; 1.09) |
| Intractability in first 5 years | 29.45 | 1 | .000 | 12.88 (5.12; 32.43) |
| Constant | 17.95 | 1 | .000 | 0.01 |
| Chi-square: 73.31 | | 5 | .000 | |
| Area under ROC: 0.88 (95% CI: 0.82-0.94) | | | .000 | |

ROC, receiver operating characteristic; CI, confidence interval.

Four subjects in our cohort had surgery. In one subject a hypothalamic hamartoma was diagnosed during FU. Surgery did not prevent this patient from becoming intractable in the last year of FU. In two patients a low-grade ganglioglioma was found during FU.
After surgery, one patient ended with seizures in the last year of FU, whereas the other never relapsed after surgery. One patient had five primarily generalized seizures before enrollment and subsequently was in remission for almost 5years. Then he had 10 acute symptomatic seizures within 1 month as a result of intracranial pressure due to a cerebellar astrocytoma. Operation was followed by remission.

**Risk factors for active epilepsy and intractability**

The following variables were significantly associated with active epilepsy and intractability in the last year of FU: epilepsy type, etiology at enrollment, number of seizures and 3-month remission in first 6 months of FU, fast response to AED, TR at 2 and 5 years, intractability in the first 5 years of FU, longest remission and number of AEDs in the first 5 years of FU (**Appendix 3: Table S1**).
In multivariate stepwise backward analysis predicting intractability, 'non-idiopathic etiology,' 'a history of febrile seizures,' 'no 3-month remission during the first 6 months of FU,' and 'intractability in the first 5 years of FU' remained in the model (**Table 4.5**). The accuracy of the model was good (area under ROC 0.88).

**Mortality**

During the first 5 years of FU nine children died. Their causes of death have been described in detail previously (Callenbach et al., 2001). After these years another nine subjects died (**Appendix 3: Table S2**). Based on 18 deaths and 6,775.4 person years of FU, the crude mortality rate was 2.7 per 1,000 person-years. Compared with the general population, the SMR was almost 10 times higher in the current cohort (SMR 9.7; 95% CI 5.7–15.3). Seventeen of the 18 who died had a remote symptomatic etiology and one had a localization-related cryptogenic etiology. The SMR of remote symptomatic etiology was 31.6 (95% CI 18.4–50.6) and was significantly higher than the SMR of idiopathic/cryptogenic etiology: 0.8 (95% CI 0.02 to 4.2).
Fourteen patients died as a result of their underlying condition, and two other patients died probably as a result of an epileptic seizure, but according to the criteria were not regarded as SUDEP (Annegers & Coan, 1999). In two other patients, the cause of death could not be established. Because SUDEP criteria were not sufficiently met and no postmortem report was available, we considered these two as ''possible SUDEP'' (Annegers & Coan, 1999). Based on these two, our SUDEP rate might have been 3/10,000 person-years of FU maximally.

## DISCUSSION

### Final outcome

Compared with the available literature, our study concerns a relatively large cohort of children with new-onset epilepsy with long-term follow-up. First of all, it demonstrates that the majority of the children had a good outcome at last contact, with 71% being in remission for at least 5 years. This finding is comparable with that of a Finnish population-based study of 144 children (Sillanpaa & Schmidt, 2006). They found a 5-year TR in 67% after a mean FU of 37 years. Our findings are also in agreement with a retrospective hospital-based Japanese study of 148 children with epilepsy (Wakamoto et al., 2000). After a mean FU of 18.9 years, 63% of their cohort achieved a 5-year TR. Considering the results of these three long-term FU studies, we conclude that the long-term outcome in childhood-onset epilepsy is favorable in about two-thirds of children.

On the other side, 8.5% of our cohort was intractable in the final year. Long-term intractability was reported in only one other study, in which at last contact 11.7% of 613 subjects were intractable after a median FU of ~10 years (Berg et al., 2006). In addition, two other studies reported on intractability, but their mean FU was only 55 months. Oskoui found 6.9% of 196 children with intractability using a stricter definition, which probably led to a lower rate, whereas Kwong found a higher rate (14.2% of 309 children), which probably resulted from more subjects with remote symptomatic etiology (40.8% vs. 27.8% in our cohort) (Kwong et al., 2003; Oskoui et al., 2005).

### Course

We analyzed the course of epilepsy by comparing three separate years during FU on the occurrence of seizures or not. The course was favorable in half of the cohort, and outcome improved in 29%. In more than one-fourth of subjects, improvement started only after 5 years of FU; 62% of these reached a 5-year TR versus 88% in subjects with earlier improvement. This suggests that late improvement leads to a worse outcome than early improvement or that more time is needed to reach remission.

The fact that remote symptomatic etiology was more frequent in the deteriorating than in the favorable group was probably the cause of their worse course and perhaps illustrates the natural course of epilepsy. In at least half of the group, deterioration began after 5 years of FU, but was not caused by age or etiological differences within this group. A poor course started already in the first half year of FU, with only a few subjects having a 3-month remission or a fast response to treatment.

We conclude that the course of epilepsy can be inconsistent. Especially improvement but also deterioration may occur after considerable time has passed. A good example is subjects with an early good course with no seizures during the first 5 years of FU or only during the first 6 months. After long remission, 17% relapsed and half of them ended with active epilepsy and some even became intractable. Short-term results and predictions of outcome should, therefore, be interpreted with caution. The question remains whether in the future such an inconsistent course can be influenced by treatment strategies to prevent deterioration or to accelerate improvement.
This brings us to the question of whether AEDs influence the course of epilepsy or merely suppress seizures. In the present study, the favorable and improving course could have been the result of treatment, although some never used AEDs and improvement sometimes was delayed for many years. In the poor group, treatment certainly was not effective and in the deteriorating group development of drug resistance or tolerance might have occurred. Like others, we found non-idiopathic etiology and young age at onset significantly associated with a poor course of epilepsy (Huttenlocher & Hapke, 1990; Kwong et al., 2003). Considering this, we think that treatment does not seem to have a major impact on the outcome of epilepsy. In our opinion, the natural course of epilepsy better explains our results, with some types of epilepsy being short-lived and others having a designated poor outcome. This is in line with the hypothesis of Shinnar and Berg, who state that the long-term prognosis of seizure disorders appears to be primarily a function of the epileptic syndrome and the underlying etiology (Shinnar & Berg, 1994). Furthermore, there is evidence from retrospective studies that untreated epilepsy can result in spontaneous remission (Placencia et al., 1994; Nicoletti et al., 2009).

**Treatment**

At the end of FU one-third of our cohort continued AEDs, not only those with active epilepsy, but also a considerable number of patients in remission (27%). At least for part of those in remission treatment was probably no longer necessary. Physicians should be aware of this; incorrectly maintaining treatment may result from a patient's steady state without seizures or noticeable side effects or it can result from infrequent visits. A trial of AED withdrawal is always justified after some seizure-free years.
The proportion of subjects continuing treatment at last contact was slightly lower in our study than in two other studies, with proportions of 45% and 42% maximally (Camfield et al., 1993; Sillanpaa & Schmidt, 2006). Differences in etiology and length of FU could explain this, together with a more reserved attitude toward AEDs through the recent years. The latter is illustrated by the fact that >13% of our cohort never used AEDs during the entire FU, which is a unique feature. Only Berg

(initially 10% without AEDs) and Camfield (3% without AEDs) reported on this (Camfield et al., 1993; Berg et al., 1999a, 2006).

One-third of our subjects had their last seizure within the first year of treatment and remained seizure free until the end of FU (early remission group). In the Finnish study, a comparable proportion of subjects started a 5-year remission within 1 year of treatment. However, half of them later relapsed (Sillanpaa & Schmidt, 2006). Another study reported that 45% of children with localization-related cryptogenic epilepsy instantly became seizure free after starting treatment (Camfield & Camfield, 2002). About 13% of our early remission group had this epilepsy type. We conclude that early remission after initiation of treatment may occur, especially in favorable epilepsy types. Yet 16% of our early remission group had a remote symptomatic etiology, meaning that part of the explanation is still lacking.

**Mortality**

The SMR in the present hospital-based study (9.7) was slightly higher compared with the 7.0 we found after 5 years of FU (Callenbach et al., 2001). The SMR for those with symptomatic etiology was 31.6. In a community-based cohort in the United States the SMR was 7.5 for the whole cohort and 33.5 for children with symptomatic etiology (Berg et al., 2004). Although we cannot compare the SMRs of these two studies, because of differences in composition of the cohorts, obviously more subjects with symptomatic etiology die (Logroscino & Hesdorffer, 2005). The finding that more subjects with symptomatic etiology die was also shown in other studies and is probably a result of the underlying severe disorder (Annegers et al., 1979; Brorson & Wranne, 1987; Sillanpaa et al., 1998; Lhatoo et al., 2001; Camfield et al., 2002).

We had two deaths in our study without a known cause. Although we are not sure if these could have been SUDEP, the maximum SUDEP rate would be 3/10,000 person-years of FU. Others reported rates between 1–2/10,000 and 4/10,000 (Donner et al., 2001; Camfield & Camfield, 2005; Weber et al., 2005).

**Advantages and limitations**

In this prospective cohort study, children with epilepsy were included and followed up since diagnosis. The size of the cohort and the length of FU are advantages of this study, in addition to the thorough panel-classification and the regular check-ups with detailed questionnaires. Not many cohorts are comparable on these points: most have fewer children (Brorson & Wranne, 1987; Kwong et al., 2003; Oskoui et al., 2005) sometimes with longer FU (Wakamoto et al., 2000; Sillanpaa & Schmidt, 2006), and those with more children have shorter FU thus far (Camfield et al., 1993; Berg et al., 2006). Furthermore, only a few studies like ours included exclusively children

with new-onset epilepsy and followed them prospectively (Berg et al., 1999b; Shinnar et al., 1999). A limitation of our study is the fact that we had regular visits only during the first 5 years. To extend FU, we sent a concise questionnaire taking little time to optimize cooperation. Wherever possible, the gathered data were supplemented with data from the medical files. However, details on dates of seizures and AED changes may have become less accurate in the course of time.

## CONCLUSIONS

The long-term prognosis of epilepsy is favorable in the majority of children, especially for those with idiopathic etiology. In contrast, epilepsy remains active in ~30% and is intractable in ~10%, and is then highly associated with non-idiopathic etiology or an early unfavorable course. During FU, the course of epilepsy can be inconsistent: periods of remission can interchange with periods of seizures. It remains to be seen whether such a course is influenced by the treatment given, since childhood-onset epilepsy is often a benign self-limiting disorder and treatment proved to be ineffective in those with active epilepsy or intractability. Mortality is significantly higher only in those with remote symptomatic etiology, and SUDEP in children is rare.

## ACKNOWLEDGMENTS

This work was supported by the Dutch National Epilepsy Fund [grant number 05-06].

The authors thank Joke Kuijpers, Linda van Leeuwen, Miranda Geelhoed, and Anne Olde Boerrigter for their help with the data collection for the extended follow-up.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclosure.

**REFERENCES**


Annegers JF, Hauser WA, Elveback LR. (1979) Remission of seizures and relapse in patients with epilepsy. Epilepsia 20:729–737.

Annegers JF, Coan SP. (1999) SUDEP: overview of definitions and review of incidence data. Seizure 8:347–352.

Arts WF, Geerts AT, Brouwer OF, Boudewijn Peters AC, Stroink H, van Donselaar CA. (1999) The early prognosis of epilepsy in childhood: the prediction of a poor outcome The Dutch study of epilepsy in childhood. Epilepsia 40:726–734.

Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, van Donselaar CA, Geerts AT. (2004) Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 127:1774–1784.

Berg AT, Levy SR, Testa FM, Shinnar S. (1999a) Treatment of newly diagnosed pediatric epilepsy: a community-based study. Arch Pediatr Adolesc Med 153:1267–1271.

Berg AT, Shinnar S, Levy SR, Testa FM. (1999b) Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia 40:445–452.

Berg AT, Shinnar S, Testa FM, Levy SR, Smith SN, Beckerman B. (2004) Mortality in childhood-onset epilepsy. Arch Pediatr Adolesc Med 158:1147–1152.

Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, DiMario F, Smith S. (2006) How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol 60:73–79.

Brorson LO, Wranne L. (1987) Long-term prognosis in childhood epilepsy: survival and seizure prognosis. Epilepsia 28:324–330.

Callenbach PM, Westendorp RG, Geerts AT, Arts WF, Peeters EA, van Donselaar CA, Peters AC, Stroink H, Brouwer OF. (2001) Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood. Pediatrics 107:1259–1263.

Camfield C, Camfield P, Gordon K, Smith B, Dooley J. (1993) Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. J Pediatr 122:861–868.

Camfield P, Camfield C. (2002) Epileptic syndromes in childhood: clinical features, outcomes, and treatment. Epilepsia 43(suppl 3):27–32.

Camfield CS, Camfield PR, Veugelers PJ. (2002) Death in children with epilepsy: a population-based study. Lancet 359:1891–1895.

Camfield P, Camfield C. (2005) Sudden unexpected death in people with epilepsy: a pediatric perspective. Semin Pediatr Neurol 12:10–14.

Donner EJ, Smith CR, Snead OC 3rd. (2001) Sudden unexplained death in children with epilepsy. Neurology 57:430–434.

Gastaut H. (1969) Classification of the epilepsies. Proposal for an international classification. Epilepsia 10(suppl):14–21.

Hauser WA, Anderson VE, Loewenson RB, McRoberts SM. (1982) Seizure recurrence after a first unprovoked seizure. N Engl J Med 307:522–528.

Huttenlocher PR, Hapke RJ. (1990) A follow-up study of intractable seizures in childhood. Ann Neurol 28:699–705.

ILAE. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 22:489–501.

ILAE. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 30:389–399.

ILAE. (1993) Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 34:592–596.

Kwong KL, Sung WY, Wong SN, So KT. (2003) Early predictors of medical intractability in childhood epilepsy. Pediatr Neurol 29:46–52.

Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JW, Shorvon SD. (2001) Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. Ann Neurol 49:336–344.

Logroscino G, Hesdorffer DC. (2005) Methodologic issues in studies of mortality following epilepsy: measures, types of studies, sources of cases, cohort effects, and competing risks. Epilepsia 46(suppl 11):3–7.

Nicoletti A, Sofia V, Vitale G, Bonelli SI, Bejarano V, Bartalesi F, Tran DS, Preux PM, Zappia M, Bartoloni A. (2009) Natural history and mortality of chronic epilepsy in an untreated population of rural Bolivia: a follow-up after 10 years. Epilepsia 50:2199–2206.

Oskoui M, Webster RI, Zhang X, Shevell MI. (2005) Factors predictive of outcome in childhood epilepsy. J Child Neurol 20:898–904.

Placencia M, Sander JW, Roman M, Madera A, Crespo F, Cascante S, Shorvon SD. (1994) The characteristics of epilepsy in a largely untreated population in rural Ecuador. J Neurol Neurosurg Psychiatry 57:320–325.

Shinnar S, Berg AT. (1994) Does antiepileptic drug therapy alter the prognosis of childhood seizures and prevent the development of chronic epilepsy? Semin Pediatr Neurol 1:111–117.

Shinnar S, O'Dell C, Berg AT. (1999) Distribution of epilepsy syndromes in a cohort of children prospectively monitored from the time of their first unprovoked seizure. Epilepsia 40:1378–1383.

Sillanpaa M, Jalava M, Kaleva O, Shinnar S. (1998) Long-term prognosis of seizures with onset in childhood. N Engl J Med 338:1715–1722.

Sillanpaa M, Schmidt D. (2006) Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 129: 617–624.

Sillanpaa M, Schmidt D. (2009) Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. Brain 132:989–998.

Stroink H, Geerts AT, van Donselaar CA, Peters AC, Brouwer OF, Peeters EA, Arts WF. (2007) Status epilepticus in children with epilepsy: Dutch study of epilepsy in childhood. Epilepsia 48:1708–1715.

Wakamoto H, Nagao H, Hayashi M, Morimoto T. (2000) Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. Brain Dev 22: 246–255.

Weber P, Bubl R, Blauenstein U, Tillmann BU, Lutschg J. (2005) Sudden unexplained death in children with epilepsy: a cohort study with an eighteen-year follow-up. Acta Paediatr 94:564–567.

**SUPPORTING INFORMATION**

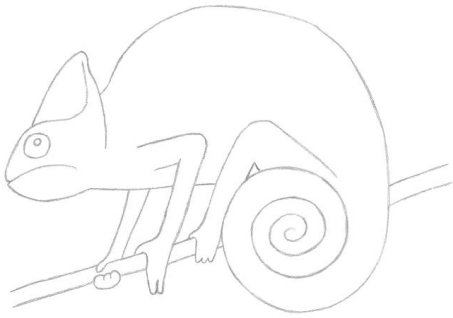
Additional Supporting Information may be found in the online version of this article or in **Appendix 3**:

**Table S1**. Significant variables for active epilepsy ($TR_E$ < 5 year) and final intractability, and odds ratios for intractability (OR) for each value as compared with the reference value of that variable.

**Table S2**. Characteristics of nine subjects who died after more than 5 years of follow-up (FU). The causes of death of those who died in the first 5 years have been described in detail previously (Callenbach et al., 2001).

**Figure S1**. Cumulative proportion reaching a 2-year terminal remission ($TR_E$) during follow-up.

# Chapter 5 Health and Social Economic Status following Childhood-Onset Epilepsy: the Dutch Study of Epilepsy in Childhood



Ada T. Geerts, Oebele F. Brouwer, Cees A. van Donselaar, Hans Stroink, A.C. Boudewijn Peters, Els A.J. Peeters, and Willem F.M. Arts

*Epilepsia (2011),* ***52*** *(12), 2192-2202*

**ABSTRACT**

Epilepsy may have far-reaching consequences for patients, other than having seizures and medication. At 15 years after diagnosis, this study investigates health perception, restrictions due to epilepsy, living arrangements (including marital status, and offspring), and the educational and occupational attainment of subjects with childhood-onset epilepsy.

A total of 453 subjects with epilepsy had a five-year follow-up since diagnosis with regular visits and data collection. Ten years later, a questionnaire addressing epilepsy was completed by 413 subjects, resulting in a mean follow-up of 15 years. Subjects were compared with age peers of the Dutch population for each etiological group separately, and also for subjects with/without a five-year terminal remission regardless of treatment. Age-adjusted standardized incidence rates were calculated for each variable.

Subjects with normal intelligence had a health perception comparable with that of the general population, but significantly more subjects without remission had a worse health perception, especially those still using medication. Restrictions and symptoms due to epilepsy were reported by 14% of the subjects, mainly by those without remission or with ongoing medication. The living arrangement of subjects with idiopathic or cryptogenic etiology was similar to that of Dutch age peers. Subjects with remote symptomatic etiology less often lived independently or with a partner, and more frequently resided in an institution or living group for the disabled. Those with and without remission were more often part of another household, mainly due (in both groups) to having a remote symptomatic etiology. Rates of having a partner and offspring were significantly reduced only for subjects with remote symptomatic etiology.

Fewer students with idiopathic/remote symptomatic etiology and students in remission followed higher vocational or scientific education. In these latter groups, the highest attained education of employees was lower than expected. The employment status of subjects with idiopathic or cryptogenic etiology was comparable with that of their Dutch age peers, but fewer subjects with remote symptomatic etiology were employed and more of them were part of the dependent population. However, for those in the labor force (employed/unemployed) all employment rates were $\geq 90\%$, even for those with remote symptomatic etiology. Nevertheless, fewer employees than expected had a higher vocational or scientific level of occupation, even those with idiopathic etiology and those in remission.

Health perception, living arrangement and socioeconomic status were influenced by epilepsy, comorbidities or treatment, particularly for subjects with remote symptomatic etiology or no remission. The group in remission fared less well than expected, mainly due to the numbers of subjects with remote symptomatic etiology in this group. In line with others, we conclude that

childhood-onset epilepsy is associated with lower educational attainment, even for subjects with idiopathic etiology and subjects in remission; probably related to this, their occupational level was also lower than expected.

## INTRODUCTION

After a diagnosis of epilepsy, the main focus is on clinical aspects, such as etiology, seizure frequency, treatment, and the subsequent prognosis. When seizures start during childhood, additional aspects become important, as epilepsy and its etiology may have consequences for cognitive, psychosocial/emotional development, education, and later employment. Moreover, epilepsy may negatively influence social functioning, self-esteem, and quality of life.

Studies investigating these aspects in cohorts with childhood-onset epilepsy report that the long-term prognosis is unfavorable in terms of level of cognition and education and rate of employment and marriage (Kokkonen et al., 1997; Sillanpaa et al., 1998; Wakamoto et al., 2000; Zelnik et al., 2001; Sillanpaa et al., 2004; Camfield & Camfield, 2008; Yu et al., 2009; Sogawa et al., 2010), and that the risk of social and educational problems is increased even for those with ‘‘epilepsy only,’’ or with idiopathic epilepsy in remission without medication (Jalava et al., 1997; Sillanpaa et al., 1998; Camfield & Camfield, 2010). In contrast, others found that normally intelligent children with epilepsy have a favorable educational and social prognosis (Wakamoto et al., 2000; Sillanpää & Schmidt, 2010), and that adults with well-controlled epilepsy (many with onset during childhood) and without other impairments or disabilities generally experience no problems with employment (Jacoby, 1995).

However, these findings remain controversial and childhood-onset epilepsy in neurologically intact children is not as innocent as it may seem. In these children, initiation of special education services often precedes the onset of seizures (Schouten et al., 2001; Berg et al., 2005), and progress at school may be worse before seizure onset, with more children having ‘‘epilepsy only’’ repeating a school year (Schouten et al., 2001). Psychiatric disorders are significantly more frequent in children with uncomplicated epilepsy than in controls (Davies et al., 2003). Moreover, MRI studies in children with epilepsy point to discrete anatomic abnormalities in those with attention deficit hyperactivity disorder (Hermann et al., 2007).

Based on these findings, more data from cohorts with long-term follow-up are required. Between 1988 and 1992, consecutively recruited children attending hospital with new-onset epilepsy were followed prospectively; course and outcome at 2, 5, and 15 years after diagnosis are already published (Arts et al., 1999, 2004; Geerts et al., 2010). Here we report the health perception and socioeconomic status for each etiologic group, and for subjects with or without 5-year terminal

remission, regardless of treatment.

## METHODS

Ethical approval for this study was obtained from the review boards of the hospitals.

### Cohort

Detailed descriptions and setting of the original prospective hospital-based study of 494 children with new-onset epilepsy have been published (Arts et al., 1999). Children were enrolled between 1988 and 1992. A panel of three pediatric neurologists classified seizures and epilepsies shortly after enrollment based on history, neurologic examination, electroencephalography (EEG), computed tomography (CT) scans, or (sometimes) magnetic resonance imaging (MRI) (Gastaut, 1969; ILAE, 1981). At 2-year follow-up, the original classifications based on older guidelines were replaced by the later classifications of the International League against Epilepsy (ILAE, 1989). Etiology was idiopathic, cryptogenic, or remote symptomatic including mental retardation (ILAE, 1993). At the end of the present study, the etiologic classifications were reconsidered as some subjects proved to have neurologic brain-related morbidities.

All subjects had had at least two unprovoked epileptic seizures or one status epilepticus before enrollment. Subjects with brain tumors and other progressive affections diagnosed at entry were excluded. Although hospital based, our recruitment rate was ~75% of the expected annual incidence in the referral area (Arts et al., 1999).

### Follow-up and questionnaire

During the first 5-year follow-up, children attended hospital at regular intervals; after this period follow-up stopped. Between 2004 and 2006, all subjects with a 5-year follow-up (n = 453) received a simple questionnaire (that did not burden the subjects too much) with items addressing epilepsy (Supporting Information A, **Appendix 1**). The questionnaire was returned by 413 subjects (response rate: 84% of the original 494 subjects). After informed consent, we also consulted the medical files of patients who still had seizures in the last year of follow-up.

### Statistical analyses

Results of the responders were compared with data of age peers from the general population in The Netherlands. Indirect standardization was used, meaning that we multiplied the age-specific rates of the Dutch population by the total number of subjects in each age group of our cohort, to calculate the number of cases that would have been expected. The sum of all observed cases in our cohort

was divided by the sum of all expected cases to yield the age-adjusted standardized incidence rate. Values >1 suggest a higher rate in the cohort than in the reference population, and <1 a lower rate. The computer-program Confidence Interval Analysis was used to calculate the standardized incidence rates, confidence intervals, and significance (Gardner & Altman, 1989; Gardner et al., 1989). The observed and expected cases, and the standardized incidence rate for each variable, can be found in Supporting Information B (**Appendix 4**). For some variables, specific groups of the cohort and of the Dutch population were used (e.g., subjects not in institutions, students, employees). Data on the Dutch population were provided by Statistics Netherlands (CBS): This is a national organization (covering many social aspects) that collects/analyzes data and publishes statistics on the general population on behalf of practice, policy, and science (CBS, 2005).

The health perception of the cohort was compared with that of Dutch age peers in the CBS Health Inquiry. This is an annual inquiry among a randomly drawn sample of approximately 10,000 subjects in private households (excluding subjects in institutions). This means that the age-specific rates for health perception are estimates; all other rates are based on absolute numbers of cases in the general population.

Health perception was categorized as ‘‘very good,’’ ‘‘good,’’ or ‘‘less than good.’’ These categories were not defined but were ‘‘interpreted’’ by each of the subjects who were giving their opinion. We present health perception and restrictions only for subjects with normal intelligence. The rationale for this is that, in the case of mental retardation, the caregivers/parents often gave answers and this was considered to be less accurate. Moreover, in the case of severe retardation it is difficult to assess restrictions due to epilepsy alone, as other morbidities are often present.

Responders were categorized according to etiology and to outcome, with both parameters as defined at the end of follow-up (**Table 5.1**). Because the groups with a 5-year terminal remission on antiepileptic drugs (AEDs) (n = 37) and with active epilepsy off AEDs (n = 22) were small, we present the results for the group with or without a 5-year terminal remission irrespective of treatment.

As most data of the CBS were available for 10-year age groups only, we excluded 28 subjects aged 12, 13, and 14 years, as their comparison with the 5- to 14-year-old age group would lead to bias. Only for ‘‘living arrangements’’ were 5-year age groups available. Occupational level was classified according to the International Standard Classification of Occupations (ISCO-88) (ISCO, 2010).

**Table 5.1: Data on subjects in the present study, by age group**

| A: Etiology at end of follow-up | 12-14 years | 15-24 years | 25-34 years | Total |
|---|---|---|---|---|
| **Idiopathic** | 9 (4.7%) | 136 (70.8%) | 47 (24.5%) | 192 [46.5%] |
| **Cryptogenic** | 2 (2.9%) | 54 (77.1%) | 14 (20.0%) | 70 [16.9%] |
| **Symptomatic** | 17 (11.3%) | 112 (74.2%) | 22 (14.6%) | 151 [36.6%] |
| **Total** | 28 (6.8%) | 302 (73.1%) | 83 (20.1%) | 413 [100%] |
| | | | | |
| **B: Outcome** | **12-14 years** | **15-24 years** | **25-34 years** | **Total** |
| **Remission (TR > 5 years )** | 19 (6.5%) | 214 (73.0%) | 60 (20.5%) | 293 [70.9%] |
| **No remission (TR < 5 years )** | 9 (7.5%) | 88 (73.3%) | 23 (19.2%) | 120 [29.1%] |
| **Total** | 28 (6.8%) | 302 (73.1%) | 83 (20.1%) | 413 [100%] |

TR: terminal remission.

**Definitions**

Terminal remission: the interval between the last seizure and the end of follow-up. From here onward the group with a 5-year terminal remission (regardless of treatment) is called the group in remission and the words ‘‘remote symptomatic’’ are abbreviated to symptomatic. Active epilepsy: at least one seizure in the last 5-year follow-up regardless of treatment (ILAE, 1993).
Children had no formal IQ testing at enrollment. Those attending special schools for the intellectually disabled were classified as mentally retarded (IQ < 70) and as having symptomatic etiology (Hauser et al., 1982). In The Netherlands, children with an IQ of 50–70 occasionally follow mainstream education, but most go to specialized schools. Employed: having a job for at least 12 h/week. Unemployed: having no job or working <12 h/week, but willing to work for at least 12 h/week, being available and actively looking for work (CBS, 2005). Dependent: not wanting or not able to work for at least 12 h/week or to work at all, not being available for work, or not actively looking for work. This definition includes students, housewives, and persons who are ill or disabled. Employment (unemployment) rate: number of employed (unemployed) individuals divided by all the employed plus unemployed individuals (i.e., the labor force).

**RESULTS**

**General**

The 413 subjects (47.2% male) had a mean age of 5.5 years (median 5.1; range 1 month–15.5 years) at onset of epilepsy and of 20.8 years (median 20.4; range 12.2–32.5) at last contact. Etiology at

enrollment was idiopathic in 50.8% of the cohort, cryptogenic in 21.3%, and symptomatic in 27.8%. At last contact the mean follow-up was 14.8 years (median 14.8, range 11.6–17.5) and 70.9% subjects had a 5-year terminal remission (61.9% off AEDs, 9.0% on AEDs). The remainder had active epilepsy (5.3% off AEDs, 23.7% on AEDs). In the last year of follow-up, 8.5% of the cohort was intractable with no remissions exceeding 3 months, despite the use of at least two AEDs (Geerts et al., 2010).

In addition to their epilepsy, 205 subjects (49.6%) reported one or more neurologic brain-related morbidities (mostly the cause of their epilepsy) or other impairments and disabilities. The brain-related morbidities included Sturge-Weber syndrome (n = 1), cerebral malformations (n = 14), inborn metabolic errors (n = 3), mental retardation (n = 112; IQ 50–70: n = 24, IQ < 50: n = 88), autism spectrum disorders (n = 16), and brain tumors diagnosed during follow-up (n = 3). Based on these results the etiology of 36 subjects changed to symptomatic at last contact (**Table 5.1**). The other impairments and disabilities included heart and coronary diseases (n = 5), chronic obstructive pulmonary diseases (n = 14), diseases of abdominal organs (n = 8), hormonal disorders (n = 5), disorders of the musculoskeletal system (n = 17), allergy and skin disorders (n = 15), deafness (n = 6), recurrent infections (n = 6), and autoimmune disorder (n = 1). Twelve subjects reported headaches and migraine, and 59 subjects reported attention deficit hyperactivity disorder, depression, fears or problems with concentration, learning, or behavior.

**Health perception**

The health perception of the cohort (excluding 112 mentally retarded subjects and 18 subjects giving no answer) is presented in **Figure 5.1**. The age-adjusted standardized incidence rates showed that more subjects without remission had a worse health perception than respondents of the CBS Health Inquiry (excluding institutionalized subjects). Furthermore, fewer subjects with cryptogenic/ symptomatic etiology reported a very good health perception.

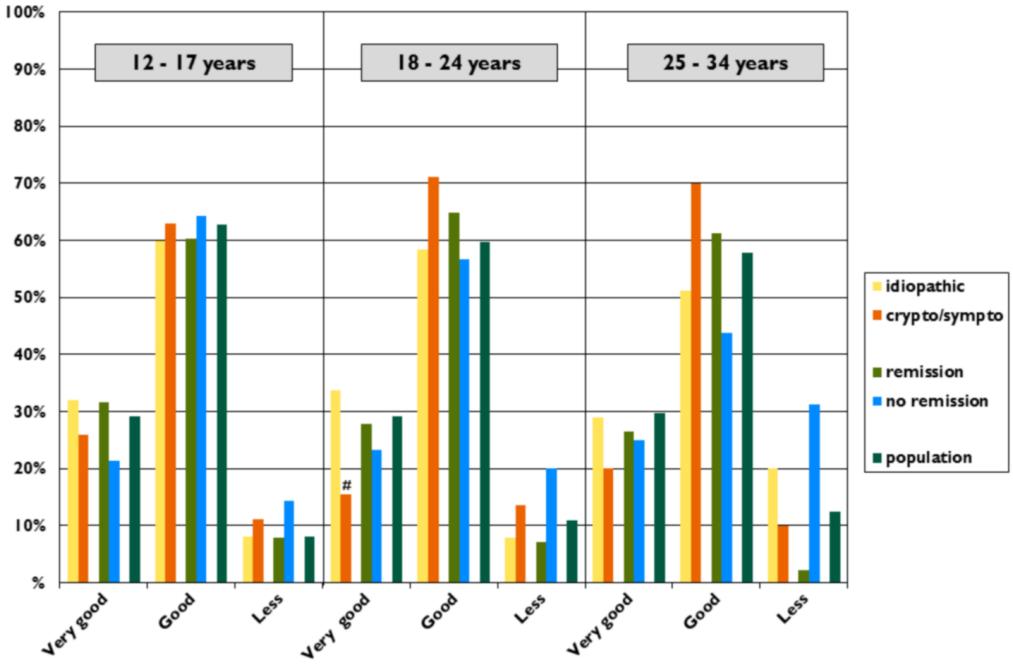
In the group without remission, more subjects still using AEDs reported a worse health perception than those off AEDs [26.7% vs. 6.7%, 95% confidence interval (CI) of difference: 1.9–38.1, $p < 0.05$).

**Restrictions**

Subjects were asked to what extent epilepsy restricted their daily activities at home, at school, or work and during sports or other leisure activities, and to what extent epilepsy restricted commuting or traveling. Some subjects reported not being allowed to do certain things, whereas others mentioned symptoms due to epilepsy that restricted them from performing certain activities. Excluding mentally retarded subjects, 42 of the 301 subjects (14.0%) reported one or more

restrictions or symptoms. Fewer subjects in remission (5.5%) reported restrictions than subjects without remission (45.3%) (Pearson $\chi^2$ 66.57, d.f. 1, $p < 0.0001$). No difference was found between the etiologic groups. Of the 68 subjects still using AEDs, 39.7% reported restrictions versus 6.4% of the 233 subjects off AEDs (Pearson $\chi^2$48.52, d.f. 1, $p < 0.0001$).

**Figure 5.1: Subjective health perception of 283 subjects (excluding those with an IQ < 70 and 18 subjects who gave no answer) compared with the respondents (excluding institutionalized subjects) of the Dutch Health Inquiry in the year 2005**




| Age-adjusted standardized incidence rates with 95% confidence interval (# p<0.1, * p<0.05). | | | |
|---|---|---|---|
| | Very good | Good | Less than good |
| Idiopathic (n=184) | 1.09 (0.83-1.41) | 0.95 (0.78-1.15) | 1.03 (0.63-1.59) |
| Cryptogenic / Symptomatic (n=99) | 0.66 (0.40-1.02)# | 1.14 (0.89-1.45) | 1.16 (0.60-2.02) |
| | | | |
| Remission (n=223) | 0.98 (0.76-1.25) | 1.04 (0.88-1.23) | 0.81 (0.49-1.27) |
| No remission (n=60) | 0.80 (0.44-1.34) | 0.92 (0.63-1.29) | 2.03 (1.08-3.46)* |

Because of small numbers, the cryptogenic (crypto) and symptomatic group (sympto) were combined. Remission: 5-year terminal remission either on or off AEDs. Numbers of subjects in the three age groups: idiopathic (50, 89, 45), cryptogenic, and remote symptomatic (27, 52, 20), remission (63, 111, 49), no remission (14, 30, 16). (#p < 0.1; indicating the difference between that group and the population).

The most often reported restrictions were related to performing activities or learning things because of concentration and memory problems, and restrictions in practicing or choosing sports, followed by having to avoid seizure triggers such as TV or alcohol. Subjects without remission mentioned restrictions regarding transportation or getting a driving license more often than those in remission (8 of 29 vs. 1 of 13 subjects, $p < 0.10$).

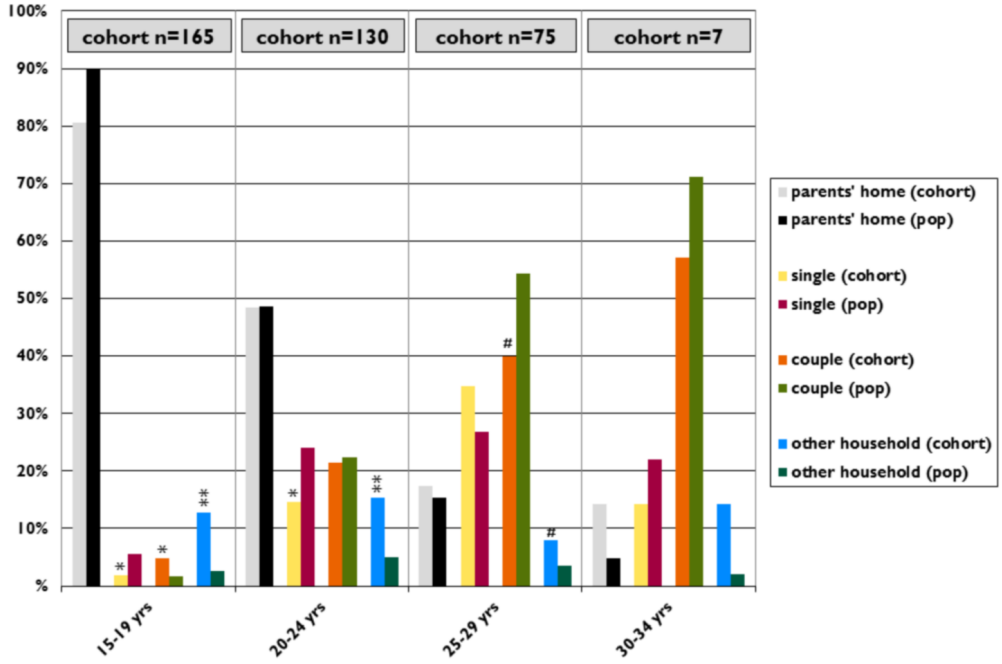
**Living arrangements**

Compared with the population, more subjects of the cohort were part of a household other than that of their family or of themselves, which resulted in significantly higher age-adjusted standardized incidence rates for both outcome groups (**Figure 5.2**). This was mainly due to subjects with symptomatic etiology of whom many lived in an institution or a living group for the disabled. About 25% of the group in remission and 50% of the group without remission had symptomatic etiology. Overall, fewer subjects with symptomatic etiology lived independently (single) or with a partner (couple). In contrast, the living arrangements of subjects with idiopathic or cryptogenic etiology and their Dutch age peers were comparable, for whom ‘‘another household’’ meant a shared house or a student home. They also resembled the Dutch population in having offspring, whereas none of the subjects with symptomatic etiology had children.

**Education**

In the age group 15–24 years, at last contact 151 subjects went to school, of which 92.7% were full time. Another 11 subjects aged ≥25, still went to school, most of them in addition to their job. Subjects with idiopathic or cryptogenic etiology resembled their Dutch age peers, although in the group with idiopathic etiology higher vocational or scientific education was slightly underrepresented (**Figure 5.3**). The latter was also true for subjects in remission and subjects with symptomatic etiology. In the latter group the rate of special education was high. Even for the group in remission the rate of special education was higher than expected. Of the 18 subjects following special education, 12 visited a specialized school for those with an IQ < 55 or an IQ of 55–70 but with additional problems, such as autism spectrum or attention deficit hyperactivity disorder. **Figure 5.4** shows the highest educational attainment of our employees (n = 137) and job seekers (n = 11), and of the Dutch labor force. In the highest age group, fewer subjects with idiopathic or remote symptomatic etiology and subjects in remission completed higher education, whereas lower education was overrepresented. The age-adjusted standardized incidence rates for higher education were lower than expected for these groups.

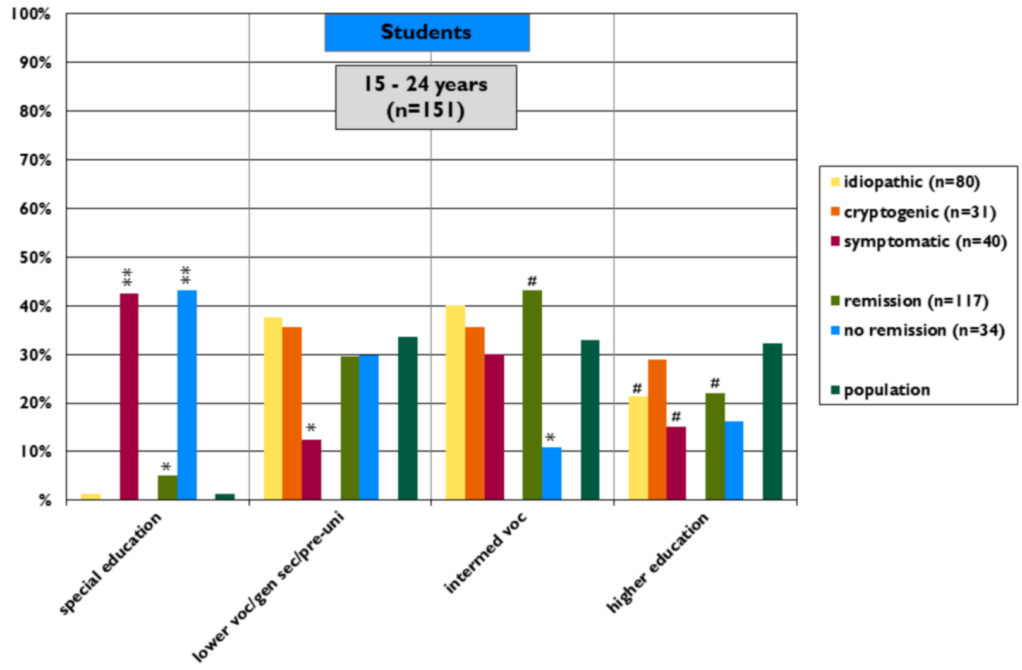
**Figure 5.2: Living arrangements of 377 subjects compared with Dutch age peers (including institutionalized subjects)**




| Age-adjusted standardized incidence rates with 95% confidence interval (** p<0.01). | | | | | |
|---|---|---|---|---|---|
| | living with parents | single | couple | other household | offspring |
| Idiopathic (n=178) | 0.91 (0.73-1.12) | 1.04 (0.71-1.47) | 1.07 (0.78-1.44) | 1.72 (0.86-3.08) | 1.20 (0.71-1.90) |
| Cryptogenic (n=67) | 0.98 (0.69-1.34) | 0.87 (0.42-1.60) | 1.21 (0.70-1.93) | 0.81 (0.10-2.92) | 1.23 (0.45-2.68) |
| Symptomatic (n=132) | 0.96 (0.76-1.19) | 0.35 (0.14-0.73)** | 0.39 (0.18-0.75)** | 7.56 (5.27-10.50)** | 0.00 |
| | | | | | |
| Remission (n=267) | 0.85 (0.64-1.10) | 0.80 (0.44-1.35) | 0.84 (0.50-1.33) | 5.42 (3.36-8.29)** | 0.89 (0.53-1.41) |
| No remission (n=110) | 0.98 (0.83-1.15) | 0.78 (0.55-1.09) | 0.92 (0.69-1.21) | 2.80 (1.85-4.08)** | 0.81 (0.30-1.76) |

Because of many data, we did not present the percentages for etiology and outcome separately in this figure. Data were unknown for eight subjects. Remission: 5-year terminal remission either on or off AEDs. (#p < 0.1, *p < 0.05, **p < 0.01, indicating the difference between that group and the population).

**Figure 5.3: Present education followed by the 151 students aged 15–24 years at the end of follow-up compared with the Dutch age peers following education (including special education, excluding institutionalized subjects) in the year 2005/2006**




Remission: 5-year terminal remission either on or off AEDs. Lower vocational (voc)/lower general secondary (gen sec)/pre-university (pre-uni) education, intermediate vocational (intermed voc) education, higher education: higher vocational or university education. (#p < 0.1, *p < 0.05, **p < 0.01, indicating the difference between that group and the population).

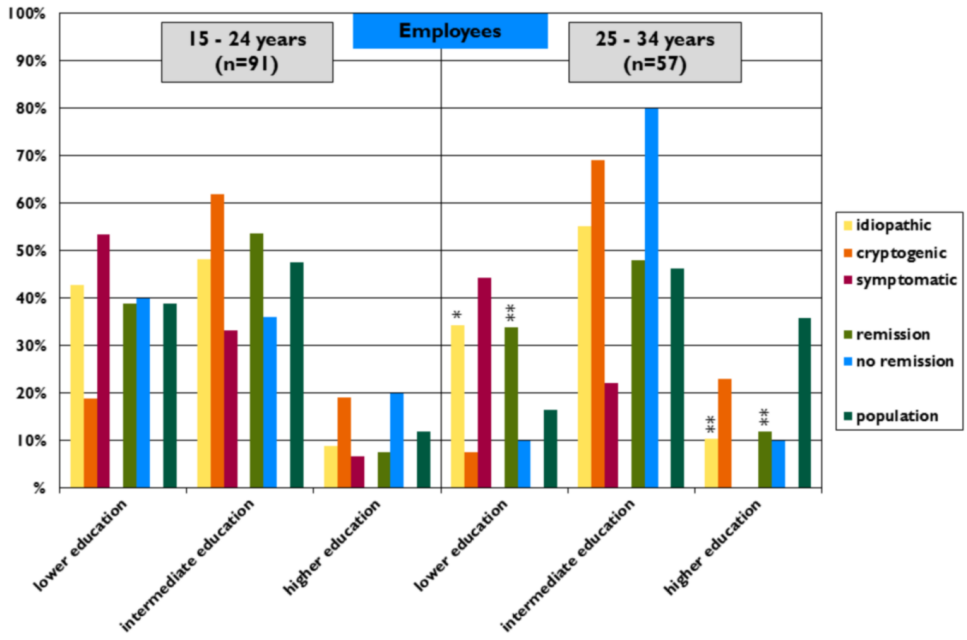
**Employment status and occupation**

The employment status for subjects with idiopathic or cryptogenic etiology resembled that of Dutch age peers, whereas fewer subjects with symptomatic etiology (excluding institutionalized subjects) were employed and more were dependent (**Figure 5.5**). Most of the latter were physically and/or mentally disabled and received a welfare pension. However, when considering only those subjects who are part of the labor force (employed or unemployed), similar employment rates were found (idiopathic 91.5%, symptomatic 91.3%, cryptogenic 97.1%, in remission 93.2%, active epilepsy 91.2%, Dutch age peers 92.0%).

A total of 139 subjects (33.7%) had a job (**Figure 5.6**). Fewer employees with idiopathic etiology had an occupation based on higher education. This was also true for employees in remission. None

of the employees with symptomatic etiology had a higher vocational or scientific job, and significantly more of them had an elementary job.

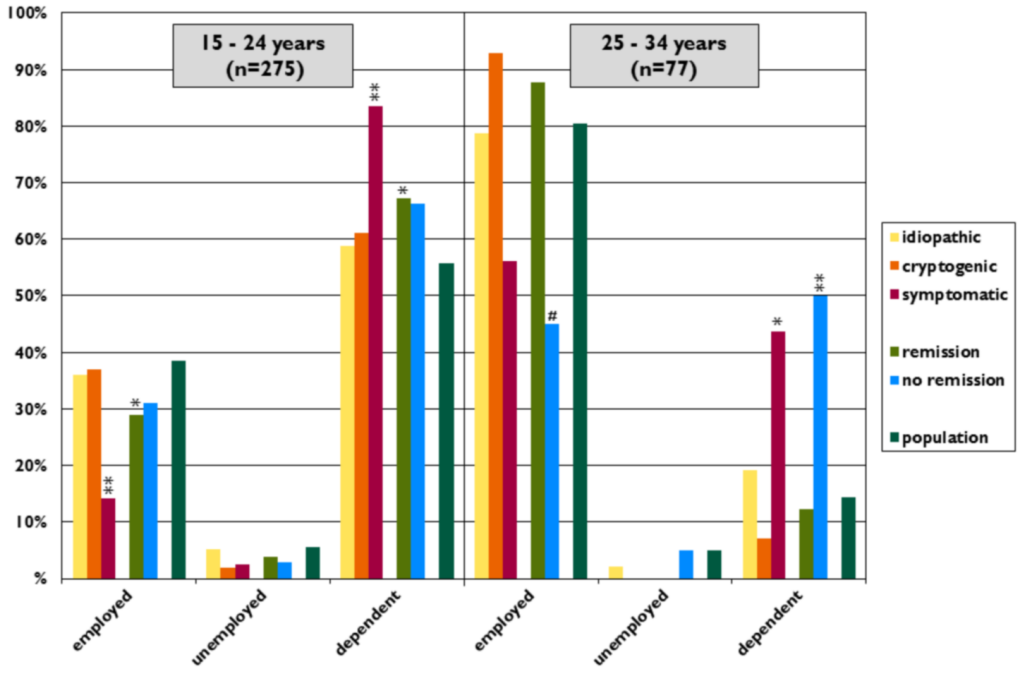
**Figure 5.4: The highest attained education of 137 employees and 11 jobseekers in our cohort compared with age peers of the labor force of the Dutch population**




| Age-adjusted standardized incidence rates with 95% confidence interval (# p<0.1, ** p<0.01). | | | |
|---|---|---|---|
| | lower education | intermediate education | higher education |
| Idiopathic (n=94) | 1.32 (0.93-1.81) | 1.09 (0.80-1.44) | 0.44 (0.20-0.84)** |
| Cryptogenic (n=34) | 0.48 (0.16-1.13) | 1.38 (0.86-2.08) | 0.97 (0.39-2.01) |
| Symptomatic (n=20) | 1.64 (0.85-2.86) | 0.62 (0.25-1.28) | 0.20 (0.01-1.11)# |
| | | | |
| Remission (114) | 1.25 (0.91-1.68) | 1.09 (0.83-1.40) | 0.42 (0.21-0.76)** |
| No remission (n=34) | 0.96 (0.48-1.73) | 1.03 (0.60-1.65) | 0.91 (0.33-1.98) |

Remission: 5-year terminal remission either on or off AEDs. Number of subjects in the two age groups: idiopathic etiology (n = 56, 38), cryptogenic (n = 21, 13), symptomatic (n = 14, 6); remission (n = 67, 47); no remission (n = 24, 10). Lower education: primary, lower vocational or lower general secondary education. Intermediate education: higher general secondary or pre-university education or intermediate vocational education. Higher education: higher vocational or university education. (*p < 0.05, **p < 0.01, indicating the difference between that group and the population).

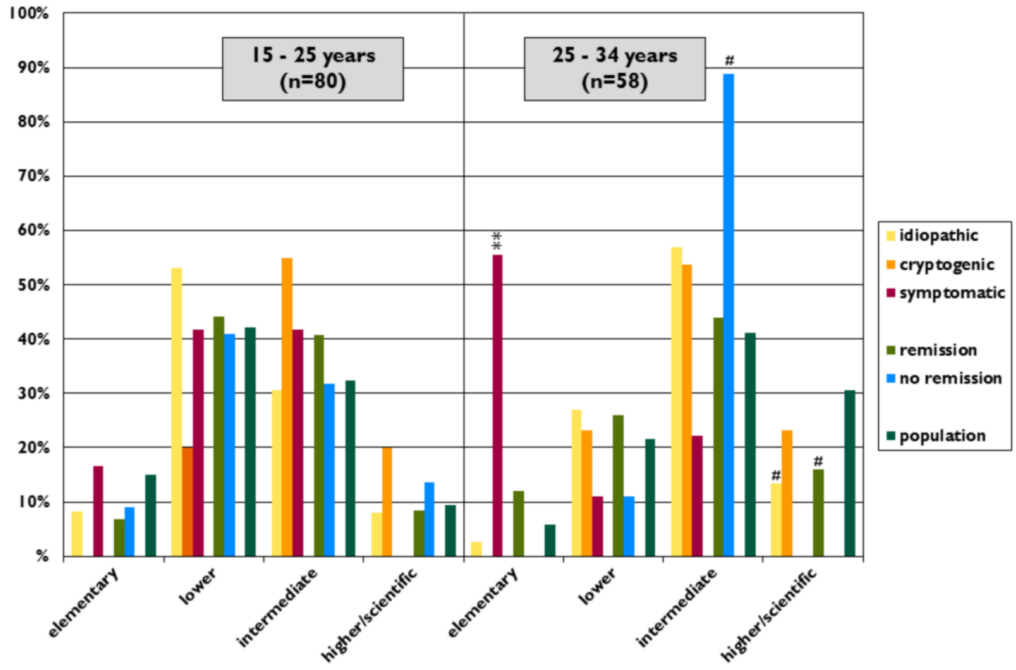
**Figure 5.5: Employment status of 352 subjects compared with the age peers of the Dutch population (excluding institutionalized subjects in the cohort and in the Dutch population)**




| Age-adjusted standardized incidence rates with 95% confidence interval (# p<0.1, * p<0.05, ** p<0.01). | | | |
|---|---|---|---|
| | Employed | Unemployed | Dependent |
| Idiopathic (n=183) | 0.95 (0.76-1.18) | 0.80 (0.35-1.58) | 1.08 (0.87-1.33) |
| Cryptogenic (n=68) | 1.03 (0.71-1.44) | 0.27 (0.01-1.50) | 1.06 (0.73-1.48) |
| Symptomatic (n=101) | 0.46 (0.29-0.70)** | 0.36 (0.04-1.30) | 1.57 (1.24-1.96)** |
| | | | |
| Remission (n=261) | 0.88 (0.72-1.06) | 0.56 (0.24-1.11) | 1.18 (0.99-1.39)# |
| No remission (n=91) | 0.71 (0.48-1.01)# | 0.60 (0.12-1.76) | 1.34 (1.02-1.74)* |

Remission: 5-year terminal remission either on or off AEDs. Number of subjects in the two age groups: idiopathic etiology (n = 136, 47), cryptogenic (n = 54, 14), symptomatic (n = 85, 16); remission (n = 204, 57); no remission (n = 71, 20). (#p < 0.1, *p < 0.05, **p < 0.01, indicating the difference between that group and the population).

**Figure 5.6: Occupational level of 138 employees in our cohort compared with that of age peers of Dutch employees**




| Age-adjusted standardized incidence rates with 95% confidence interval (# p<0.1, ** p<0.01). | | | | |
|---|---|---|---|---|
| | Elementary | Lower | Intermediate | Higher/scientific |
| Idiopathic (n=86) | 0.52 (0.17-1.22) | 1.26 (0.88-1.74) | 1.16 (0.81-1.60) | 0.56 (0.26-1.07)# |
| Cryptogenic (n=32) | 0.00 | 0.62 (0.25-1.28) | 1.52 (0.90-2.41) | 1.19 (0.48-2.45) |
| Symptomatic (n=20) | 3.00 (1.21-6.19)* | 0.86 (0.31-1.86) | 0.92 (0.37-1.90) | 0.00 |
| | | | | |
| Remission (n=108) | 0.85 (0.41-1.56) | 1.09 (0.78-1.49) | 1.16 (0.85-1.55) | 0.62 (0.33-1.06)# |
| No remission (n=30) | 0.52 (0.06-1.89) | 0.89 (0.43-1.64) | 1.39 (0.78-2.29) | 0.62 (0.13-1.81) |

The occupation of two other employees was unknown. Number of subjects in the two age groups: idiopathic etiology (n = 49, 37), cryptogenic (n = 19, 13), symptomatic (n = 12, 8); remission (n = 59, 49); no remission (n = 21, 9). Elementary: jobs with simple duties. Lower: jobs with duties at the level of preliminary vocational education. Intermediate: jobs with duties at the level of intermediate vocational education. Higher/scientific: jobs with duties at the level of higher vocational or scientific education. (#p < 0.1, **p < 0.01, indicating the difference between that group and the population).

## DISCUSSION

This study examined the health and socioeconomic status of subjects with new-onset epilepsy, diagnosed in childhood and followed prospectively for a mean of 15 years. By comparing our subjects with age peers of the Dutch population, we aimed to reveal the long-term consequences of epilepsy other than seizures and medication.

The results are presented for each etiologic subgroup separately, because cohorts generally include subjects with varying types of epilepsy and etiology, and with divergent prognoses. Comparing the entire cohort as one group with the general population would yield less meaningful results, and makes comparison with other cohorts difficult.

In the group with idiopathic etiology, we were particularly interested in whether their life (without neurologic impairments or disabilities) would revert to normal once they reached long-term remission without medication. However, this group did less well than their Dutch age peers, even though 75% were in remission and off AEDs, and their health perception, living arrangements, and numbers of offspring were comparable. Although their employment rate was not lower than expected, they had lower educational and occupational levels. This could be due to the epilepsy and seizures (Baker et al., 2011), or to an assumed preexisting common cause for the epilepsy and other brain dysfunctions. Based on reports from our group and others (Schouten et al., 2001; Oostrom et al., 2003), we tend to opt for the latter possibility. Moreover, two recent studies showed that minor dysfunctions/disabilities were present not only in children with epilepsy but also in their healthy siblings (Clarke et al., 2007; Wandschneider et al., 2010). These findings support the hypothesis that dysfunctions or disabilities are part of the epileptic spectrum and are (at least in part) genetically determined (Berg, 2011; Jensen, 2011). We expected that the group with cryptogenic etiology would show at least similar results. However, subjects in this small group showed few differences with the Dutch population; they bore more resemblance to the idiopathic group than to the symptomatic group (which had the worst results).

Besides etiology, we chose to present the results for two distinct outcome groups, as we hypothesized that the largest group would be the one including subjects whose epilepsy was (probably) a temporary, age-related experience. This group was expected to have a longstanding remission, mostly without AEDs, and most are expected to have normal intelligence and at first glance seem to live their life without restrictions. The other smaller group would fare much worse, with active epilepsy, still using AEDs, and many subjects almost certainly with obvious disabilities, and often depending on state welfare. Although not all of these aspects proved to be true, the distinction between a relatively good and a poor long-term outcome is clear.

Nevertheless, in the present study, the group in remission performs less well than expected. Although their health perception was good and they reported significantly fewer restrictions than subjects without remission, more were part of the dependent population and part of another household (mainly due to those subjects with symptomatic etiology). In addition, students and employees in remission less often followed or completed higher education, resulting in lower job levels; this is not surprising, since about 50% of this group had idiopathic etiology with similar results, and about 25% had symptomatic etiology with worse results.
The group with active epilepsy confirmed our expectations. Their health perception was significantly worse, they reported more restrictions and were more often disabled and institutionalized; >50% had symptomatic etiology. For those able to study, the level of education was lower, although for employees no significant differences were found in highest attained education and level of occupation, probably due to the small numbers.

**Health perception**

In a population-based birth-cohort study, children with epilepsy with good cognitive development without comorbidities have similar adult health compared to the unaffected population (Chin et al., 2011). A Finnish study comparing subjects with childhood-onset epilepsy with matched controls also found no significant difference in health perception; the study showed that 8.3% of 96 subjects with ‘‘epilepsy only’’ had a poor self-assessed health status (Jalava & Sillanpaa, 1997a). This result is similar to the 11% of our 184 subjects with idiopathic etiology reporting a worse health perception, the main reasons for this being active epilepsy and ongoing medication. This effect of medication was also found in another study, but only for subjects on polytherapy (Jalava et al., 1997).

**Marriage or cohabitation, offspring**

Several cohort studies of childhood-onset epilepsy reported a lower rate of marriage or cohabitation for subjects with uncomplicated epilepsy or normal intelligence (Jalava & Sillanpaa, 1997b; Wakamoto et al., 2000; Sillanpää et al., 2004; Chin et al., 2011), and for non-institutionalized patients (Kokkonen et al., 1997). In our study, however, subjects with idiopathic or cryptogenic etiology did not differ regarding marriage/cohabitation from the Dutch population (apart from our symptomatic group).
In three studies on childhood-onset epilepsy, subjects with uncomplicated epilepsy had fewer children than expected (Jalava & Sillanpaa, 1997b; Sillanpaa et al., 2004; Chin et al., 2011). In the present study, the group with symptomatic etiology had fewer children, whereas the idiopathic and cryptogenic groups were similar to the general population. Although our results look promising, one

reason for these divergent outcomes might be that most studies used matched controls, whereas we made a comparison with the Dutch population, which is probably less accurate.

**Education**

Similar to the present study, many studies on childhood-onset epilepsy reported a lower than average educational attainment for subjects with epilepsy (Kokkonen et al., 1997; Sillanpaa et al., 1998, 2004; Wakamoto et al., 2000; Koponen et al., 2007); however, one study was partly based on prevalent cases and could have been biased toward more severe epilepsy (Jalava et al., 1997). Most of the latter studies also reported this trend for subjects with ‘‘epilepsy only,’’ normal intelligence, and for those in remission and off AEDs. As argued previously, these findings are not unexpected, since there is increasing evidence that mild impairment of cognitive functions likely precedes the onset of epilepsy, even in cases with ‘‘epilepsy only’’ (Schouten et al., 2001; Oostrom et al., 2003; Berg et al., 2005; Henkin et al., 2005; Vinayan et al., 2005; Beghi et al., 2006; Hermann et al., 2007; Taylor et al., 2010). Our finding that subjects reported concentration and memory problems concurs with this. These results are one of the reasons why the phrase ‘‘epilepsy only’’ or ‘‘just epilepsy’’ should be avoided (Berg, 2011).

**Employment status**

Several studies reported on the employment rates of subjects with childhood-onset epilepsy. Two studies found that the employment rates were not significantly lower for subjects with epilepsy (Kokkonen et al., 1997; Wakamoto et al., 2000), whereas others reported a lower employment rate (Jalava et al., 1997; Sillanpaa et al., 1998; Koponen et al., 2007). This was even found for those who were seizure free and without medication for many years (Sillanpää et al., 1998).

We found that the employment status of subjects with idiopathic or cryptogenic etiology did not differ from that of the general population, but significantly fewer subjects with symptomatic etiology were employed. However, when considering the labor force of our cohort the unemployment rates were low, even for those with symptomatic etiology. Some studies found a higher unemployment rate for subjects with epilepsy (Jalava et al., 1997; Kokkonen et al., 1997; Koponen et al., 2007). Sillanpaa et al. (2004) found that the risk of being unemployed in subjects in remission off medications was not significantly higher than that in controls; however, in those still taking medication, the risk was high and was the same whether or not the subjects were in remission.

The contradictory results in employment and unemployment rates described above could be due to the small sample sizes, or to differences in definitions and control groups. Our ‘‘better’’ results might also be explained by the Dutch system in which slightly disabled persons are allowed to work

under special guidance in so-called ‘‘social workshops.’’ More studies are needed to elucidate this topic, preferably in large cohorts with matched controls that are prospectively followed.

**Occupation**

Few studies reported on the level of occupation, although this is an important issue. In the present cohort, relatively fewer subjects had a job with a higher/scientific level. Another important issue is underemployment. In one study, subjects with ‘‘epilepsy only’’ were significantly more often underemployed compared with controls (Jalava et al., 1997). In that study, ‘‘underemployment’’ meant that the level of education and training was significantly higher than the requirement for the present job. Of their patients, 23% were underemployed versus 9% of random controls, and 14% of employee controls. In our cohort, 26% of employees had a job one or two levels beneath their educational level, which is comparable to that found by Jalava et al. We were unable to compare possible underemployment in our cohort with that of the Dutch population because these data were not available for the corresponding Dutch age groups. We recommend that underemployment should be investigated in future cohort studies.

**Considerations**

Some of the strengths and weaknesses of this study have been reported previously (Geerts et al., 2010). Even though this study was hospital based, we think this prospectively followed cohort is a representative sample of patients diagnosed with childhood-onset epilepsy. Both the recruitment rate, which was approximately 75% of the expected annual incidence in the referral area, as well as the relatively low proportion with symptomatic etiology at enrollment (28%) support this. Two other prospective hospital based studies reported rates of 18% and 26% at enrollment (Berg et al., 1999; Shinnar et al., 1999). We think our cohort is not biased toward more severe cases, as children with progressive disorders were excluded when diagnosed at the time of inclusion. If such a diagnosis was made during follow-up, that patient was retained in the study. Furthermore, in The Netherlands, severe epilepsy patients with other impairments or disabilities are frequently institutionalized before the onset of epilepsy and are treated in these specialized institutions and not elsewhere.

As we had no matched controls, we compared our subjects with Dutch age peers. Statistics Netherlands provide their data in 5- or 10-year age groups. In our cohort, because the age group 25–34 years was skewed to the left with more subjects of younger age, this may have influenced the comparisons; therefore, differences found in the highest age group may be less significant than reported. We think that only the comparison regarding occupational level may have been influenced, with fewer subjects having had a chance to achieve a higher level occupation.

## CONCLUSIONS

Based on these results we conclude that, even after long-term follow-up, childhood-onset epilepsy has a substantial impact on many aspects of life, especially for those with symptomatic etiology or with active epilepsy. For those with idiopathic etiology, the impact is less severe, but still significant with regard to educational and occupational achievement.


## ACKNOWLEDGMENTS

The Dutch National Epilepsy Fund provided a grant for this study (no. 05-06). None of the authors has any conflict of interest to disclose.


## DISCLOSURE

All authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## REFERENCES


Arts WF, Geerts AT, Brouwer OF, Peters AC, Stroink H, Van Donselaar CA. (1999) The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood. Epilepsia 40:726–734.

Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, Van Donselaar CA, Geerts AT. (2004) Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 127:1774–1784.

Baker GA, Taylor J, Aldenkamp AP. (2011) Newly diagnosed epilepsy: cognitive outcome after 12 months. Epilepsia 52:1084–1091.

Beghi M, Beghi E, Cornaggia CM, Gobbi G. (2006) Idiopathic generalized epilepsies of adolescence. Epilepsia 47(Suppl. 2):107–110.

Berg AT. (2011) Epilepsy, cognition, and behavior: the clinical picture. Epilepsia 52(Suppl. 1):7–12.

Berg AT, Shinnar S, Levy SR, Testa FM. (1999) Newly diagnosed epilepsy in children: presentation at diagnosis. Epilepsia 40:445–452.

Berg AT, Smith SN, Frobish D, Levy SR, Testa FM, Beckerman B, Shinnar S. (2005) Special education needs of children with newly diagnosed epilepsy. Dev Med Child Neurol 47:749–753.

Camfield C, Camfield P. (2008) Twenty years after childhood-onset symptomatic generalized epilepsy the social outcome is usually dependency or death: a population-based study. Dev Med Child Neurol 50:859–863.

Camfield P, Camfield C. (2010) Idiopathic generalized epilepsy with generalized tonic-clonic seizures (IGE-GTC): a population-based cohort with >20 year follow up for medical and social outcome. Epilepsy Behav 18:61–63.

CBS (Dutch Central Bureau of Statistics). (2005) Dutch Central Bureau of Statistics. Available at: http://www.cbs.nl.

Chin RF, Cumberland PM, Pujar SS, Peckham C, Ross EM, Scott RC. (2011) Outcomes of childhood epilepsy at age 33 years: a population-based birth-cohort study. Epilepsia 52:1513–1521.

Clarke T, Strug LJ, Murphy PL, Bali B, Carvalho J, Foster S, Tremont G, Gagnon BR, Dorta N, Pal DK. (2007) High risk of reading disability and speech sound disorder in rolandic epilepsy families: case–control study. Epilepsia 48:2258–2265.

Davies S, Heyman I, Goodman R. (2003) A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol 45:292–295.

Gardner MJ, Altman DG. (1989) Statistics with confidence – confidence intervals and statistical guidelines, British Medical Journal, London.

Gardner MJ, Gardner SB, Winter PD. (1989) Confidence interval analysis (CIA) microcomputer program manual. British Medical Journal, London.

Gastaut H. (1969) Classification of the epilepsies. Proposal for an international classification. Epilepsia 10(Suppl.):14–21.

Geerts A, Arts WF, Stroink H, Peeters E, Brouwer O, Peters B, Laan L, Van Donselaar C. (2010) Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood. Epilepsia 51:1189–1197.

Hauser WA, Anderson VE, Loewenson RB, McRoberts SM. (1982) Seizure recurrence after a first unprovoked seizure. N Engl J Med 307:522–528.

Henkin Y, Sadeh M, Kivity S, Shabtai E, Kishon-Rabin L, Gadoth N. (2005) Cognitive function in idiopathic generalized epilepsy of childhood. Dev Med Child Neurol 47:126–132.

Hermann B, Jones J, Dabbs K, Allen CA, Sheth R, Fine J, McMillan A, Seidenberg M. (2007) The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. Brain 130:3135–3148.

ILAE. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 22:489–501.

ILAE. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 30:389–399.

ILAE. (1993) Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 34:592–596.

ISCO (The International Standard Classification of Occupations). (2010) The International Standard Classification of Occupations. Available at: ttp://www.ilo.org/public/english/bureau/stat/isco/index.htm.

Jacoby A. (1995) Impact of epilepsy on employment status: findings from a UK study of people with well-controlled epilepsy. Epilepsy Res 21:125–132.

Jalava M, Sillanpaa M. (1997a) Physical activity, health-related fitness, and health experience in adults with childhood-onset epilepsy: a controlled study. Epilepsia 38:424–429.

Jalava M, Sillanpaa M. (1997b) Reproductive activity and offspring health of young adults with childhood-onset epilepsy: a controlled study. Epilepsia 38:532–540.

Jalava M, Sillanpaa M, Camfield C, Camfield P. (1997) Social adjustment and competence 35 years after onset of childhood epilepsy: a prospective controlled study. Epilepsia 38:708–715.

Jensen FE. (2011) Epilepsy as a spectrum disorder: implications from novel clinical and basic neuroscience. Epilepsia 52(Suppl. 1):1–6.

Kokkonen J, Kokkonen ER, Saukkonen AL, Pennanen P. (1997) Psychosocial outcome of young adults with epilepsy in childhood. J Neurol Neurosurg Psychiatry 62:265–268.

Koponen A, Seppala U, Eriksson K, Nieminen P, Uutela A, Sillanpaa M, Hyvarinen L, Kalviainen R. (2007) Social functioning and psychological well-being of 347 young adults with epilepsy only – population-based, controlled study from Finland. Epilepsia 48:907–912.

Oostrom KJ, Smeets-Schouten A, Kruitwagen CL, Peters AC, Jennekens-Schinkel A. (2003) Not only a matter of epilepsy: early problems of cognition and behavior in children with ‘‘epilepsy only’’ – a prospective, longitudinal, controlled study starting at diagnosis. Pediatrics 112:1338–1344.

Schouten A, Oostrom K, Jennekens-Schinkel A, Peters AC. (2001) School career of children is at risk before diagnosis of epilepsy only. Dev Med Child Neurol 43:575–576.

Shinnar S, O’Dell C, Berg AT. (1999) Distribution of epilepsy syndromes in a cohort of children prospectively monitored from the time of their first unprovoked seizure. Epilepsia 40:1378–1383.

Sillanpaa M, Jalava M, Kaleva O, Shinnar S. (1998) Long-term prognosis of seizures with onset in childhood. N Engl J Med 338:1715–1722.

Sillanpaa M, Haataja L, Shinnar S. (2004) Perceived impact of childhood-onset epilepsy on quality of life as an adult. Epilepsia 45:971–977.

Sillanpaa M, Schmidt D. (2010) Long-term employment of adults with childhood-onset epilepsy: a prospective population-based study. Epilepsia 51:1053–1060.

Sogawa Y, Masur D, O'Dell C, Moshe SL, Shinnar S. (2010) Cognitive outcomes in children who present with a first unprovoked seizure. Epilepsia 51:2432–2439.

Taylor J, Kolamunnage-Dona R, Marson AG, Smith PE, Aldenkamp AP, Baker GA. (2010) Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment? Epilepsia 51:48–56.

Vinayan KP, Biji V, Thomas SV. (2005) Educational problems with underlying neuropsychological impairment are common in children with Benign Epilepsy of Childhood with Centrotemporal Spikes (BECTS). Seizure 14:207–212.

Wakamoto H, Nagao H, Hayashi M, Morimoto T. (2000) Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. Brain Dev 22:246–255.

Wandschneider B, Kopp UA, Kliegel M, Stephani U, Kurlemann G, Janz D, Schmitz B. (2010) Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. Neurology 75:2161–2167.

Yu PM, Ding D, Zhu GX, Hong Z. (2009) International Bureau for Epilepsy survey of children, teenagers, and young people with epilepsy: data in China. Epilepsy Behav 16:99–104.

Zelnik N, Sa'adi L, Silman-Stolar Z, Goikhman I. (2001) Seizure control and educational outcome in childhood-onset epilepsy. J Child Neurol 16:820–824.

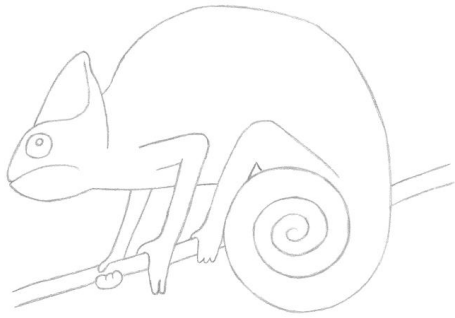
**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article or in **Appendix 1 and 4**:

Supporting Information A: Questionnaire Epilepsy Research.

Supporting Information B: Several tables show the observed and expected cases, and the standardized incidence rate for each variable.

# Chapter 6 Onset of intractability and its course over time: the Dutch Study of Epilepsy in Childhood



Ada T. Geerts, Oebele F. Brouwer, Hans Stroink, Cees A. van Donselaar, A.C. Boudewijn Peters, Els A.J. Peeters, and Willem F.M. Arts

*Epilepsia (2012),* ***53*** *(4), 741-751*

**ABSTRACT**

Intractability in epilepsy is difficult to define, and little is known about its onset, course, and duration. We investigated these aspects (as well as the occurrence of intractability) during long-term follow-up in patients with epilepsy, focusing on possible explanations for the variation in time of onset and duration of intractability.

After diagnosis, 453 patients with childhood-onset epilepsy had a 5-year follow-up with regular visits and data collection. Ten years later they received a questionnaire with items concerning epilepsy, which was completed by 413 patients resulting in a mean follow-up of 15 years. Intractability during the first 5 years was compared with that in the last year of follow-up. Intractability was defined as having no 3-month remission during a 1-year period despite adequate medical treatment.

At least 12.1% of the cohort had a period of intractability during the 15-year follow-up, and 8.5% were intractable in the final year. Of the patients with idiopathic etiology 4.3% had a period of intractability versus 17.0% for those with cryptogenic, and 22.6% for those with remote symptomatic etiology ($p < 0.001$). Other risk factors at baseline were younger age at first seizure, generalized cryptogenic/symptomatic or localization-related symptomatic epilepsy, mental retardation, and febrile convulsions before enrollment. The cumulative risk of a period of intractability was 6.1% (95% confidence interval [CI] 3.7–8.5) at 2 years follow-up and 8.2% (95% CI 5.4–11.0) at 5 years. The mean time to onset of intractability during the first 5 years of follow-up was 1.6 (95% CI 1.3–2.0; median 1.0) years and the mean duration of intractability during these 5 years was 3.3 (95% CI 2.8–3.8; median 3.6) years. Fifteen patients were intractable only during the first 5 years of follow-up (group A), and 19 subjects were intractable both during the first 5 years and the last year of follow-up (group B). Compared with group A, group B had shorter remission and a longer time to intractability during the first 5 years and more were intractable in the fifth year of follow-up. Sixteen other patients had a late onset of intractability after 5 years of follow-up, sometimes after long periods of remission (group C). No significant differences in baseline characteristics were found among groups A, B, and C, but slightly more children in groups B and C became mentally retarded during the follow-up. In all groups, antiepileptic drugs were of little use in preventing and ending intractability.

There is a large unpredictable variation in time of onset, course, and duration of intractability, with a higher chance of final intractability after a poor course during the first 5 years of follow-up. The natural course of epilepsy probably best explains the variable course of intractability. The effect of medication seems to be minor.

## INTRODUCTION

Recent studies indicate that the course of childhood-onset epilepsy may vary during long-term follow-up. Periods of remission and periods with frequent seizures can interchange (Berg et al., 2004, 2006; Sillanpää & Schmidt, 2006a; Berg et al., 2009; Geerts et al., 2010). The end of an episode with frequent seizures could result from the effectiveness of treatment, or from the self-limiting character of some types of epilepsy. Conversely, persistent seizures (or so-called intractability) starting late in the course of epilepsy could result from poor adherence with the prescribed treatment, from development of drug resistance or tolerance, or from an ongoing process of epileptogenesis that is insensitive to treatment (Loscher & Schmidt, 2006; Abou-Khalil, 2007; Brown et al., 2009; Vervloet et al., 2011).

Studying the course of intractability, especially its time of onset and the interchanging pattern with periods of remission, may enable one to find explanations for the development, discontinuation, or chronicity of intractability, and to distinguish the natural course of epilepsy from treatment effects. Between 1988 and 1992, we recruited 494 consecutive children who presented at the hospital with new-onset epilepsy. Results of the clinical course at 2 and 5 years after diagnosis have been published (Arts et al., 1999, 2004) as well as the results of 413 patients with a mean 15-year follow-up (Geerts et al., 2010); this latter publication presented risk factors for final intractability (non-idiopathic etiology, febrile seizures before enrollment, no 3-month remission in the first 6 months of follow-up, and having a period of intractability during the first 5 years of follow-up). This report focuses on the course of intractability during follow-up and possible reasons for its variation. A comparison is made between intractability in the first 5 years and intractability in the final year.

## METHODS

The methods of this study have been reported in detail elsewhere (Geerts et al., 2010). There follows a brief overview.

### Setting

Between 1988 and 1992, four hospitals in The Netherlands recruited 494 children aged 1 month to 16 years with newly diagnosed epilepsy. The ethical committees of the participating hospitals approved the study. Written informed consent was provided by all parents and children aged ≥12 years. This Dutch Study of Epilepsy in Childhood had a recruitment rate approximating 75% of the expected annual incidence in the referral area. Excluded from the study were children with

seizures as a result of brain tumors or other progressive diseases diagnosed at the time of recruitment.

**Follow-up**

Of the original cohort, 453 subjects had a 5-year follow-up with regular visits and data collection. Ten years later, they received a simple questionnaire (that did not burden the subjects too much) with items addressing epilepsy, such as date of the very last seizure, use of antiepileptic drugs (AEDs) at last contact and, if applicable, date of AED discontinuation. When subjects reported seizures in the last year of follow-up, we contacted their treating physician or checked their medical records to determine intractability in the final year. This means that only the information covering the first 5 years and the last year of follow-up was sufficiently detailed to investigate intractability. Non-responders were contacted again and the final response rate based on the original 494 patients was 84%. Of the 413 respondents, 47.2% was male. Mean age at epilepsy onset was 5.5 years (median 5.1, range 0.0–15.5) years. Mean follow-up was 14.8 years (median 14.8, range 11.6–17.5) years.

**Classifications**

All seizures and epilepsies were classified at enrollment and, if necessary, revised after 2 years using the seizure, etiology, and epilepsy classifications of the International League against Epilepsy (Gastaut, 1969; ILAE, 1981, 1989, 1993). Etiology at enrollment was idiopathic in 50.8%, cryptogenic in 21.3%, and remote symptomatic including mental retardation (intelligence quotient [IQ] < 70) in 27.8%. At the end of the present study, the etiologic classifications were checked again, as some patients proved to have neurologic brain-related morbidities.

**Definitions**

Intractability: no remission exceeding 3 months (at least one seizure per 3 month) during a minimum period of 1 year of observation despite adequate treatment (Arts et al., 2004). Adequate treatment: optimal choice and use of at least two AEDs, either alone or in combination. AED intolerance or allergy was not considered as failure. To make the analysis pragmatic, we calculated the duration of intractability as the interval between the first and last seizure of a period with at least one seizure per 3 month. Early onset of intractability: onset of intractability within the first 5 years of follow-up. Late onset of intractability: onset after the first 5 years of follow-up. Fast response to medication: 6 months of remission starting within 2 months after initiation of AED. Longest remission: maximum interval between seizures. Terminal remission: interval between the very last seizure and the end of follow-up. A 5-year terminal remission was reached by 71% of the cohort.

**Statistics**

To investigate possible differences between groups, Chi-square statistics were used in case of categorical variables and one-way analysis of variance (ANOVA) in case of continuous variables. For the risk of intractability we used Kaplan-Meier survival statistics. Log rank (Mantel-Cox) was used to test for equality of the survival distributions for the different types of epilepsy.

## RESULTS

### Entire follow-up

**Figure 6.1** shows how many subjects were intractable during the 15-year follow-up and at which points in time. At least 50 patients had a period of intractability (12.1%): in 34 subjects it started during the first 5 years of follow-up (8.2% with early onset) and in 16 other subjects it started later and was present during the last year of follow-up (3.9% with late onset). In the last year of follow-up a total of 35 patients were intractable (8.5% of 413). The mean follow-up of these 35 patients did not differ from those that were not intractable in the final year (14.6 vs. 14.8 years, ANOVA: $F = 0.698$, d.f. = 1, $p = 0.40$), neither did the median follow-up (14.5 [range 13.0–16.8] years versus 14.9 [range 11.6–17.5] years), independent samples median test: $p = 0.22$).

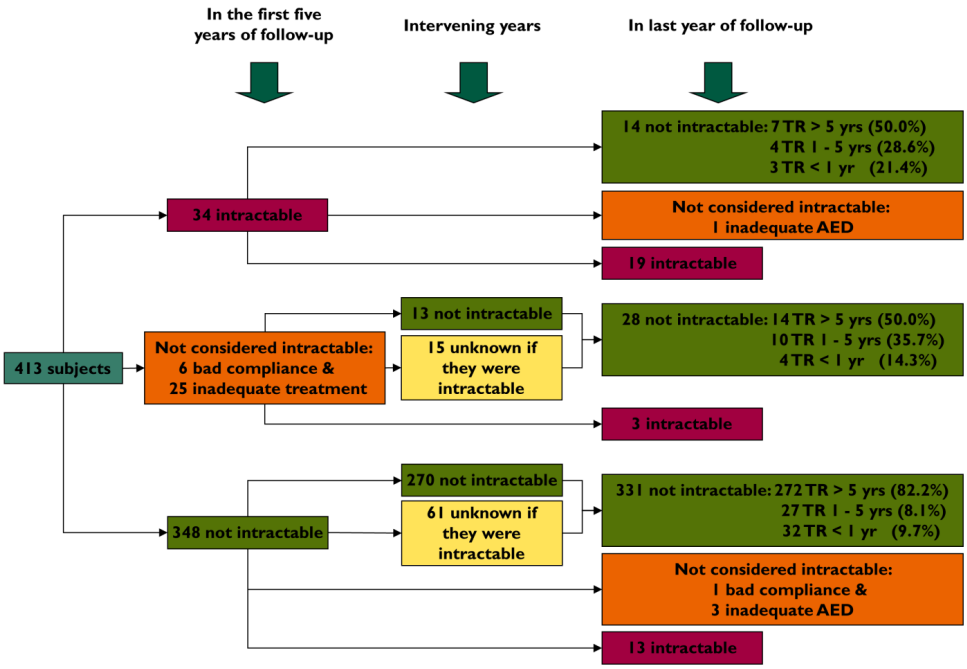
Another 31 patients with frequent seizures during the first 5 years were not considered intractable during that particular period despite their seizure pattern, because of insufficient compliance (n = 6), or inadequate treatment (n = 25), according to our definition of intractability (**Figure 6.1**). The same is true for four patients with inadequate treatment in the last year of follow-up and one patient with insufficient compliance in that year. For all the patients with inadequate treatment (no optimal choice and use of at least two AEDs) there was a plausible reason.

Between the first 5 years and the last year of follow-up (intervening years: **Figure 6.1**), 283 patients (13 + 270) had definitely not been intractable during this period as could be derived from the date of their last seizure or AED discontinuation. The remaining 76 patients (15 + 61) may have had a period of intractability in these intervening years. This means that the proportion of patients with at least one period of intractability during the entire 15-year follow-up ranges from a minimum of 12.1% definite intractable cases (34 + 3 + 13 = 50 of 413) to a possible maximum of 30.5% (34 + 3 + 13 + 15 + 61 = 126 of 413).

### Intractability during the first 5 years of follow-up

During these years, the mean time to onset of intractability was 1.6 (95% confidence interval [CI] 1.3–2.0, median 1.0) years, and its mean duration was 3.3 (95% CI 2.8–3.8, median 3.6) years.

**Figure 6.1: Flowchart of patients with or without intractability during a mean follow-up of 15 years** (TR, terminal remission).




The cumulative risk of intractability was 6.1% (95% CI 3.7–8.5) at 2 years of follow-up, and 8.2% (95% CI 5.4–11.0) at 5 years. **Figure 6.2 (A, B)** shows the Kaplan-Meier curves for several types of epilepsy according to the classifications of the ILAE and of Berg et al. (ILAE, 1989; Berg et al. 2006). Using the ILAE classification, there was a significant difference between the curves in **Figure 6.2A** (Log rank [Mantel-Cox] $\chi^2 = 33.78$, d.f. = 6, $p < 0.0001$). Those with West syndrome or Lennox-Gastaut syndrome or epilepsy with myoclonic absences or myoclonic-astatic seizures (generalized cryptogenic and/or symptomatic epilepsies) had the highest risk of intractability in the first 5 years, whereas none of the patients with localization-related idiopathic etiology had a period of intractability. Using the Berg classification, the difference between the three curves in **Figure 6.2B** was also significant (log rank [Mantel-Cox] $\chi^2 = 27.24$, d.f. = 3, $p < 0.0001$). However, the difference between the focal (localization-related cryptogenic and symptomatic groups) and catastrophic (West syndrome or Lennox-Gastaut syndrome, epilepsy with myoclonic-astatic seizures or myoclonic absences, epilepsies and syndromes undetermined whether focal or generalized) curves was only marginally significant (log rank [Mantel-Cox] $\chi^2 = 3.44$, d.f. = 1, $p = 0.064$).

**Figure 6.2: (A, B) Time course and cumulative risk of intractability during the first 5 years of follow-up for different types of epilepsy.**

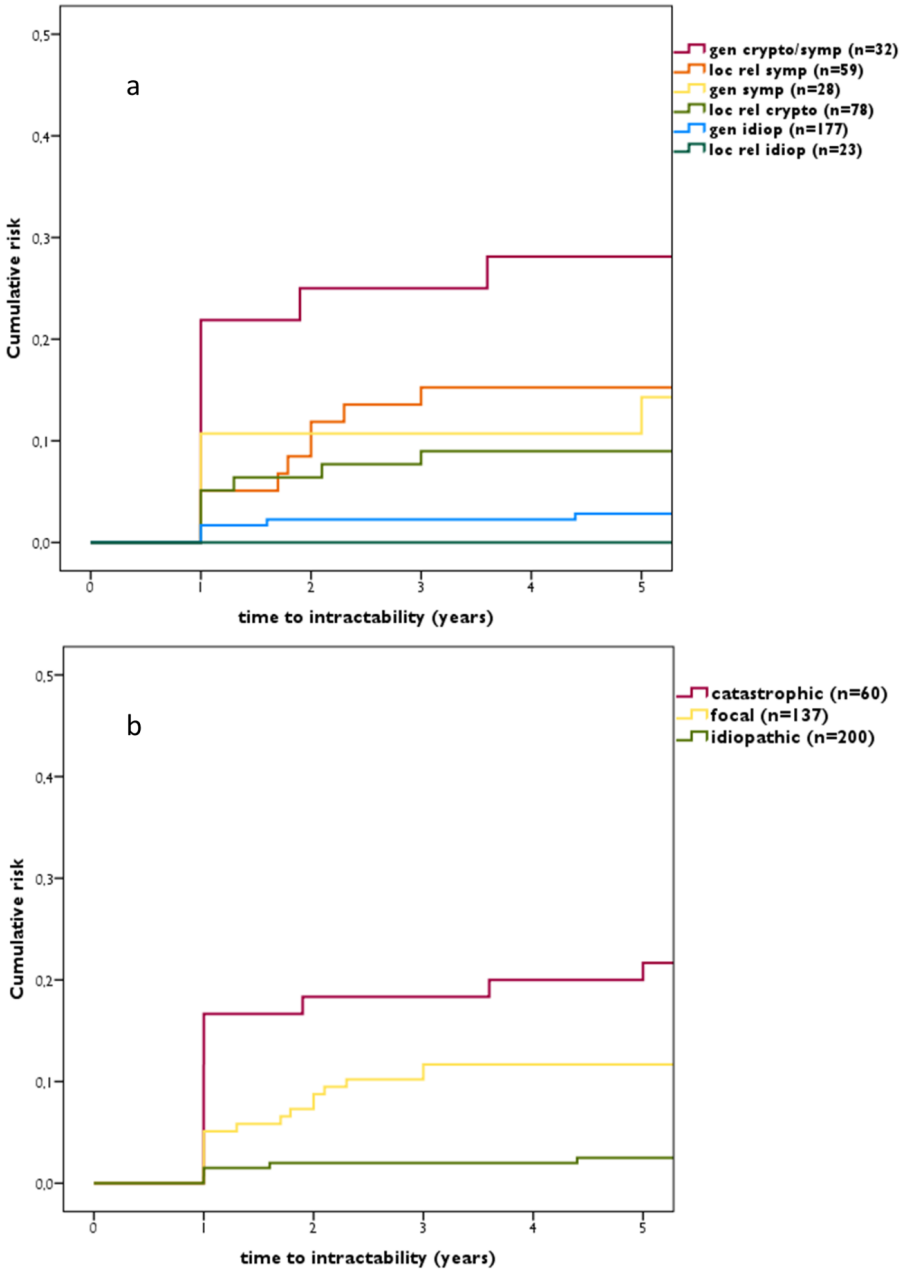


**Figure 6.2**: (A) Gen crypto/symp, generalized cryptogenic, and/or symptomatic epilepsies and syndromes (West syndrome; Lennox-Gastaut syndrome, epilepsy with myoclonic-astatic seizures or with myoclonic absences); loc rel symp, localization-related symptomatic epilepsies and syndromes; gen symp, generalized symptomatic epilepsies and syndromes; loc rel crypto, localization-related cryptogenic epilepsies and syndromes; gen idiop, generalized idiopathic epilepsies and syndromes; loc rel idiop, localization-related idiopathic epilepsies and syndromes. None of the rest group (n = 16) became intractable in these years (not in figure). (B) Catastrophic, all cryptogenic and symptomatic generalized epilepsies, and epilepsies with both focal and generalized features; focal, cryptogenic and symptomatic focal; idiopathic, partial, and generalized forms of idiopathic epilepsy.

Of the focal group, 11.7% developed intractability during the first 5 years versus 21.7% of the catastrophic group. Time to onset of intractability during the first 5 years of follow-up did not differ between patients with focal epilepsy and those with catastrophic epilepsy (independent samples Mann-Whitney U-test: $p = 0.149$).

**Risk factors**

Of the patients with idiopathic etiology, 4.3% had a period of intractability either during the first 5 years and/or last year of follow-up, whereas this was 17.0% for those with cryptogenic and 22.6% for those with remote symptomatic etiology ($p < 0.001$). Other risk factors at baseline were younger age at first seizure, type of epilepsy (generalized cryptogenic/symptomatic, localization-related symptomatic), mental retardation at enrollment, and febrile convulsions before enrollment (**Table 6.1**).

**Three intractability groups**

We distinguished three groups of subjects with intractability: 15 subjects with intractability during the first 5 years only (group A), 19 subjects with intractability during both the first 5 years and the final year (group B), and 16 subjects with intractability during the final year but not during the first 5 years (group C). The mean follow-up of group A, B, and C, and the group without intractability, showed no significant differences (14.8, 14.4, 14.9, and 14.8 years, respectively, ANOVA: $F = 0.648$, d.f. = 3, $p = 0.59$); neither did the median follow-up (14.7 [range 13.3–16.8] years, 14.4 [range 13.0–16.4] years, 14.9 [range 13.2–16.8] years, and 14.9 [range 11.6–17.5] years, independent samples median test: $p = 0.33$). A summary of the individual course of epilepsy and treatment effects on the 15 patients in group A is presented in **Table S1** (**Appendix 5**). Eleven patients were seizure free in the last year of follow-up; seven of them even had a 5-year terminal remission.

**Table 6.1. Baseline characteristics and variables collected during follow-up in relation to the three intractability groups. The last three columns present the statistical significance of possible differences found in the pairwise comparison of the groups with intractability**

| **Baseline** | Intractability[1] during 15years<br><br>(n=50) | Intractable in the first five years only<br><br>**A** (n=15) | Intractable in the first five & last year of follow-up<br>**B** (n=19) | Intractable in the last year of follow-up only<br>**C** (n=16) | **A / B** | **A / C** | **B / C** |
|---|---|---|---|---|---|---|---|
| Age at first seizure: (mean years (median; range) | * | 5.1 (3.4; 0.2-13.5) | 4.1 (2.7; 0-15.3) | 4.1 (3.1; 0.1-11.6) | ns | ns | ns |
| Type of epilepsy: | *** | | | | ns | ns | ns |
| - generalized idiopathic (n=177) | 8 (4.5%) | 3 (1.7%) | 2 (1.1%) | 3[a] (1.7%) | | | |
| - generalized symptomatic (n=28) | 4 (14.3%) | 2 (7.1%) | 2 (7.1%) | 0 | | | |
| - generalized cryptogenic / symptomatic (n=32) | 13 (40.6%) | 3 (9.4%) | 6 (18.8%) | 4 (12.5%) | | | |
| - localization related idiopathic (n=23) | 0 | 0 | 0 | 0 | | | |
| - localization related symptomatic (n=59) | 13 (22.0%) | 5 (8.5%) | 4 (6.8%) | 4 (6.8%) | | | |
| - localization related cryptogenic (n=78) | 12 (15.4%) | 2 (2.6%) | 5 (6.4%) | 5 (6.4%) | | | |
| - rest (n=16) | 0 | 0 | 0 | 0 | | | |
| Type of epilepsy (Berg et al., 2006): | *** | | | | ns | ns | ns |
| - idiopathic (n=200) | 8 (4.0%) | 3 (1.5%) | 2 (1.0%) | 3 (1.5%) | | | |
| - focal (n=137) | 25 (18.2%) | 7 (5.1%) | 9 (6.6%) | 9 (6.6%) | | | |
| - catastrophic (n=60) | 17 (28.3%) | 5 (8.3%) | 8 (13.3%) | 4 (6.7%) | | | |
| - rest (n=16) | 0 | 0 | 0 | 0 | | | |
| Etiology at enrollment: | *** | | | | ns | ns | ns |
| - idiopathic (n=210) | 9 (4.3%) | 3 (1.4%) | 3 (1.4%) | 3 (1.4%) | | | |
| - remote symptomatic (n=115) | 26 (22.6%) | 9 (7.8%) | 9 (7.8%) | 8 (7.0%) | | | |
| - cryptogenic (n=88) | 15 (17.0%) | 3 (3.4%) | 7 (8.0%) | 5 (5.7%) | | | |
| Mentally retarded at enrollment: | *** | | | | ns | ns | ns |
| - yes (n=86) | 20 (23.3%) | 7 (8.1%) | 7 (8.1%) | 6 (7.0%) | | | |
| - no (n=327) | 30 (9.2%) | 8 (2.4%) | 12 (3.7%) | 10 (3.1%) | | | |
| Febrile convulsions before enrollment: | * | | | | ns | ns | ns |
| - yes (n=42) | 9 (21.4%) | 2 (4.8%) | 5 (11.9%) | 2 (4.8%) | | | |
| - no / unknown (n=371) | 41 (11.1%) | 13 (3.5%) | 14 (3.8%) | 14 (3.8%) | | | |
| Status epilepticus before enrollment: | ns | | | | ns | ns | ns |
| - yes (n=31) | 3 (9.7%) | 0 | 1 (3.2%) | 2 (6.5%) | | | |
| - no (n=382) | 47 (12.3%) | 15 (3.9%) | 18 (4.7%) | 14 (3.7%) | | | |
| Positive family history for epilepsy: | ns | | | | ns | ns | ns |
| - positive (n=55) | 8 (14.5%) | 1 (1.8%) | 5 (9.1%) | 2 (3.6%) | | | |
| - negative / unknown (n=358) | 42 (11.7%) | 14 (3.9%) | 14 (3.9%) | 14 (3.9%) | | | |
| EEG at enrollment: | ns | | | | ns | ns | ns |
| - normal (n=101) | 12 (11.9%) | 3 (3.0%) | 6 (5.9%) | 3 (3.0%) | | | |
| - epileptiform abnormalities (n=244) | 30 (12.3%) | 9 (3.7%) | 12 (4.9%) | 9 (3.7%) | | | |
| - other abnormalities (n=68) | 8 (11.8%) | 3 (4.4%) | 1 (1.5%) | 4 (5.9%) | | | |

| **During follow-up** | Intractability[1] during 15years (n=50) | Intractable in the first five years only **A** (n=15) | Intractable in the first five & last year of follow-up **B** (n=19) | Intractable in the last year of follow-up only **C** (n=16) | **A / B** | **A / C** | **B / C** |
|---|---|---|---|---|---|---|---|
| Number of seizures < AED (59 subjects no AEDs): | # | | | | ns | ns | ns |
| - 10 or less (n=167) | 16 (9.6%) | 6 (3.6%) | 5 (3.0%) | 5 (3.0%) | | | |
| - > 10 (n=169) | 31 (18.3%) | 7 (4.1%) | 14 (8.3%) | 10 (5.9%) | | | |
| - unknown (n=18) | 3 (16.7%) | 2 (11.1%) | 0 | 1 (5.6%) | | | |
| > 25 Seizures in first 6 months of follow-up: | *** | | | | ns | ns | # |
| - yes (n=150) | 29 (19.3%) | 10 (6.7%) | 13 (8.7%) | 6 (4.0%) | | | |
| - no (n=263) | 21 (8.0%) | 5 (1.9%) | 6 (2.3%) | 10 (3.8%) | | | |
| Longest remission[b]: (mean years (median; range) | *** | 1.1 (0.6; 0.1-3.4) [c] | 0.6 (0.4; 0.0-2.0) | 2.2 (1.6; 0.7-4.7) | # | * | *** |
| $TR_5$: (mean years (median; range) | *** | 0.7 (0.1; 0.0-3.4) [d] | 0.2 (0; 0.0-2.0) [e] | 0.9 (0.1; 0.0-4.7) | # | ns | # |
| Int. intake-first AED: (mean months (med.; range) | ns | 0.5 (0.03; 0-5.1) | 1.9 (0.16; 0-19.7) | 2.0 (0.2; 0-16.9) | ns | ns | ns |
| Int. intake-second AED: (mean months (med.; range) | - | 3.8 (1.4; 0-16) | 9.4 (4.2; 0-43) | 13.1 (3.9; 0-56.7) [c] | ns | # | ns |
| Fast response to AED (59 subjects no AEDs): | *** | | | | ns | ns | ns |
| - yes (n=150) | 6 (4.0%) | 2 (1.3%) | 1 (0.7%) | 3 (2.0%) | | | |
| - no (n=204) | 44 (21.6%) | 13 (6.4%) | 18 (8.8%) | 13 (6.4%) | | | |
| Time to intract.[b]: (mean years (median; range) | - | 1.2 (1.0; 1.0-2.3) | 2.0 (1.3; 1.0-5.0) | unknown | * | - | - |
| Duration of intract.[b]: (mean years (median; range) | - | 3.1 (3.2; 1.0-4.9) | 3.4 (3.9; 1.0-5.0) | unknown | ns | - | - |
| Number of AEDs [b]: (mean (median; range) | *** | 5.1 (5.0; 2-9) | 4.7 (4.0; 2-8) | 2.4 (2.0; 1-4) | ns | *** | *** |
| Polytherapy [b]: (59 subjects no AEDs): | *** | | | | ns | ** | *** |
| - yes (n=90) | 40 (44.4%) | 14 (15.6%) | 19 (21.1%) | 7 (7.8%) | | | |
| - no (n=264) | 10 (3.8%) | 1 (0.4%) | 0 | 9 (3.4%) | | | |
| Intractable during the 5th year (n=19): | - | 4 (21.1%) | 15 (78.9%) | 0 | ** | - | - |
| Status epilepticus during follow-up: | *** | | | | ns | ns | ns |
| - yes (n=5) | 4 (80%) | 1 (20.0%) | 2 (40.0%) | 1 (20.0%) | | | |
| - no (n=408) | 46 (11.3%) | 14 (3.4%) | 17 (4.2%) | 15 (3.7%) | | | |
| Mentally retarded during follow-up: | *** | | | | ns | ns | ns |
| - yes (n=32) | 10 (31.3%) | 1 (3.1%) | 5 (15.6%) | 4 (12.5%) | | | |
| - no (n=381) | 40 (10.5%) | 14 (3.7%) | 14 (3.7%) | 12 (3.1%) | | | |
| Etiology at end of follow-up: | *** | | | | | | |
| - idiopathic (n=192) | 6 (3.1%) | 2 (1.0%) | 2 (1.0%) | 2 (1.0%) | ns | ns | ns |
| - remote symptomatic (n=151) | 36 (23.8%) | 11 (7.3%) | 14 (9.3%) | 11 (7.3%) | ns | ns | ns |
| - cryptogenic (n=70) | 8 (11.4%) | 2 (2.9%) | 3 (4.3%) | 3 (4.3%) | ns | ns | ns |

[1]: either during the first five years and / or during the last year of follow-up. [a]: later reclassified to non-idiopathic epilepsy, [b]: in the 1st 5 years of follow-up, [c]: (n=12), [d]: (n=14), [e]: (n=18), $TR_5$ : terminal remission at five years of follow-up, intract.: intractability, int. : interval, -: not possible or not meaningful to calculate.
#p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001.

For five patients of group A, we found a plausible explanation for the ending of their intractability, that is, seizures were abolished or the frequency was reduced after the introduction of a new AED in four patients and after a successful temporal lobectomy in one patient (**Table 6.2**).
In group B (with intractability both during the first 5 years and the final year), 16 of the 19 patients used AEDs during the entire follow-up and had no substantial periods of remission and 50% had daily to monthly seizures. All patients in group B were considered to be drug resistant (**Table 6.2**).
**Table S2** (**Appendix 5)** describes the individual course of epilepsy for the 16 patients with late onset of intractability (group C). Seven had remissions in the first 5 years, ranging from 2.4 to 4.7 years. Nine patients even discontinued AEDs after remission during the first 5 years of follow-up, but all had recurrences and restarted medication (**Table 6.2**); in four of them reinstitution of treatment failed to regain remission. This was the only possible explanation we found for the late onset of intractability in group C. At the end of follow-up, 8 of the 16 patients of group C were drug-resistant for about 3–8 years.

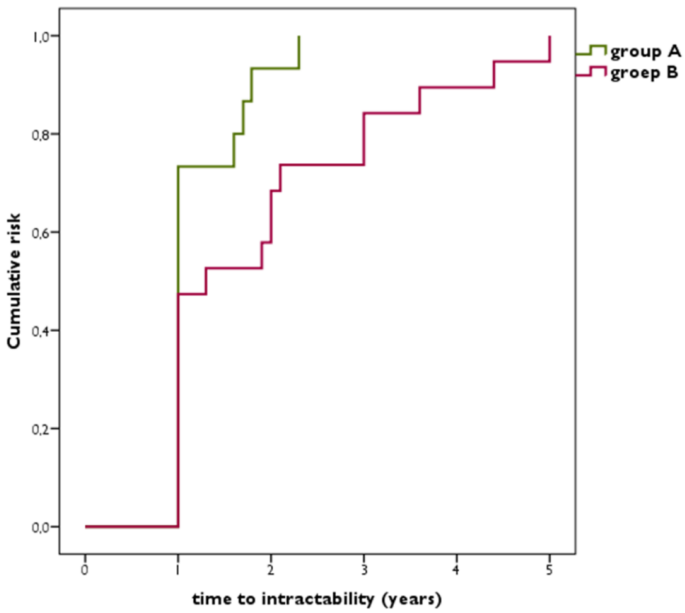
**Table 6.2. Possible explanations for temporary, continuing or late onset of intractability**

| | Temporary Group A (n=15) | Continuing Group B (n=19) | Late onset Group C (n=16) |
|---|---|---|---|
| Effect of a new AED | 4 | | |
| Effect of a new AED, but not enough to be seizure free in the last year | 1 | | |
| Effect of temporal lobectomy | 1 | | |
| No treatment effect | 9 | 16 | |
| 3-year remission while on AEDs but relapsed | | 1 | |
| Parietal arachnoid cyst: AED no effect. Five-year remission after drain removal. Relapse after 2 years without AEDs. Reinstitution of AEDs no effect. | | 1 | |
| Stop AED after remission: AED failed after relapse | | 1 | 4 |
| Stop AED after remission: AED successful after relapse, but later on intractable | | | 4 |
| Stop AED after remission: AED effect unknown after relapse and later on intractable | | | 1 |
| Deteriorated without an obvious reason | | | 7 |

To unravel why there was such a large variation in time of onset and duration of intractability, we focused on differences between these three groups that might explain this variation. The three groups did not differ in baseline characteristics (**Table 6.1**), indicating that the risk for patients to fall into any of the three groups was similar. However, during follow-up, patients of group B had a

significantly longer time to intractability (**Table 6.1, Figure 6.3**) and, consequently, more were intractable in the fifth year of follow-up and had a shorter terminal remission; they also had a slightly shorter longest remission during the first 5 years compared with those of group A. Comparison of group A with the two groups that were intractable in the last year of follow-up (groups B + C) showed a tendency for a higher proportion of patients in the latter two groups to develop mental retardation during follow-up: one of 15 (6.7%) versus 9 of 35 (25.7%) (95% CI of difference 2.9–35.2, p <0.1). The significant differences found in the comparisons of group A and B with group C were all inherent to the poor results of groups A and B during the first 5 years.

**Figure 6.3: Time course and cumulative risk of intractability during the first 5 years of follow-up for the group with temporary intractability and for the group both intractable during the first 5 years and the last year of follow-up.**




Test of equality of survival distributions: log rank (Mantel-Cox) v2 = 6.06, d.f. = 1, p = 0.014.
Group A: only intractable during first 5 years; group B: intractable during both the first 5 years and the last year.

## DISCUSSION

The present study was a pragmatic investigation. Our main interest was the time of onset of intractability, its course over time, and the variables that might influence it. The definition of intractability itself was not the issue; any other definition could have been used and probably would have yielded similar results.

Unfortunately, our results and the resulting conclusions are limited by the lack of data on the onset of intractability in the period after the fifth year of follow-up. Nevertheless, we think that the data provide valuable insight into the onset and course of intractability during the long-term follow-up of our cohort, even though intractability in some years could not be established. However, in our opinion, the latter is not a significant drawback. In fact, if all subjects with possible intractability in the intervening years had been intractable, our conclusions about a fluctuating course and temporary intractability would have been strengthened. The main outcome of this prospective study is that at least 12% of our cohort with childhood-onset epilepsy experienced a period of intractability during a 15-year follow-up since diagnosis, and 8.5% were intractable in the final year. The majority became intractable within 5 years after epilepsy onset, but approximately 50% of the patients were no longer intractable at the last contact; some even reached a 5-year terminal remission. Other patients had a late onset of intractability after 5 years of follow-up, and in some, intractability was interrupted by long periods of remission. This has also been reported by others (Takenaka et al., 2000; Sillanpää & Schmidt, 2006a). These findings show that time of onset, course, and duration of intractability vary considerably between subjects. According to the present study, these aspects of intractability are hardly predictable, even though intractability itself can be predicted to a certain extent. The risk factors for intractability found in the present study (younger age at onset, remote symptomatic etiology, type of epilepsy, and mental retardation) have also been reported by others (Huttenlocher & Hapke, 1990; Berg et al., 1996; Casetta et al., 1999; Kwong et al., 2003; Altunbasak et al., 2007). However, in the present study none of these risk factors were associated with a temporary, continuing, or late onset of intractability. In practice this means that a treating physician can only estimate the risk of intractability for an individual patient, but not the time of onset or duration of intractability, and the sustainability of remission following intractability. Especially for surgery candidates, it would have been valuable if these aspects of intractability could have been predicted.

### Intractability as a temporary phenomenon

The finding that intractability can be followed by remission has also been reported by others (Berg et al., 2006, 2009; Callaghan et al., 2007, 2011; Choi et al., 2008, 2011), and some state that the

natural history of intractable seizures in children follows a gradual line of slow improvement, especially in patients with normal intelligence (Huttenlocher & Hapke, 1990). In our opinion this might particularly apply to children with a period of intractability early in the course of their epilepsy.

In a prevalence cohort study of adults with intractable epilepsy no clear predictors for remission were found (Choi et al., 2008, 2011), whereas in a similar study, developmental delay, symptomatic generalized epilepsy, longer duration of intractability, and number of failed AEDs were negatively associated with remission, although in multivariate analysis only the number of failed AEDs remained significant (Callaghan et al., 2011). In a prospective childhood-onset study, idiopathic epilepsy and lower seizure frequency were positively associated with remission (Berg et al., 2009). In the present study no clear predictors were found for temporary intractability versus ongoing or repeating intractability. However, although the numbers were small, there were some significant differences between subjects with temporary intractability and those intractable again at the end, indicating that the epilepsy of the latter patients was probably more severe from the beginning and deteriorated further during follow-up.

It has been shown that remission after intractability started after medication changes in 28–76% of adult subjects, although the relapse rate was high (Luciano & Shorvon, 2007; Callaghan et al., 2011; Choi et al., 2011). In our cohort, we found a medication effect in 27% (4 of 15) of patients with temporary intractability, with 2 of the 4 subsequently entering terminal remission for at least 10 years. In our cohort, apart from the patients with a positive effect of AEDs or surgery, and the patient not considered intractable in the final year, we think that the improvement resulted from the natural course of the patients' epilepsy.

**Late-onset intractability**

More than 30% of our intractable patients had a late onset of intractability, starting 5 years or more after diagnosis; this has also been reported by others (Berg et al., 2003; Berg, 2004; Sillanpää & Schmidt, 2006a). Three years or more after diagnosis, Berg et al. (2006) found a late-onset intractability in 32% of children meeting their stringent definition of intractability. This occurred even after long periods of remission, a result that was confirmed in the present study. In line with this, Sillanpää et al. found a worsening course in 14% of their cohort, defined as a relapse occurring after a 5-year remission without regaining a final 5-year terminal remission (Sillanpää & Schmidt, 2006a). So far, no clear explanation for the occurrence of late-onset intractability is available, although a poorer adherence to medication during follow-up might be one (Sabaté, 2003). In addition, AED failure after restart has been reported as a possible reason (Takenaka et al., 2000;

Schmidt & Loscher, 2005; Sillanpää & Schmidt, 2006b). Two studies found that reinstitution of medication that worked for years failed to achieve control in one of three or four relapsed patients (Bouma et al., 2002; Sillanpää & Schmidt, 2006b). In our study this occurred in five patients. During ongoing treatment, mechanisms such as developing drug tolerance or resistance might lead to deterioration or intractability. However, it remains uncertain whether late-onset intractability or a worsening course results from these mechanisms, or from the progressive nature of some types of epilepsy (Takenaka et al., 2000; Abou-Khalil, 2007). In view of this, we doubt that late-onset intractability is a temporary phenomenon, like part of the early-onset intractability, but rather that it might be severe and persistent.

One study found evidence of a later onset of intractability in patients with focal epilepsy compared with those with catastrophic epilepsy (Berg et al., 2006). In our cohort, we found that slightly more patients with catastrophic epilepsy developed intractability during the first 5 years of follow-up (mostly during the first year) compared with those with focal epilepsy, but that there was no significant difference in the time to intractability. In addition, during the entire follow-up, the difference in intractability between these two groups was not significant (focal 18.2% vs. catastrophic 28.3%, Pearson's $\chi^2$: 2.53, d.f. = 1, p = 0.112), unless they would have been temporarily intractable 5 years or more after enrollment. We conclude that our results do not convincingly support the findings of Berg et al., although the trend pointed in the same direction. In the study of Berg et al., more subjects with catastrophic epilepsy developed intractability during the first 5 years of follow-up than in our study (stringent definition: approximately 50.% vs. 21.7%, respectively), although for those with focal epilepsy the numbers were the same (approximately 10% vs. 11.7%). In our cohort, the difference between the catastrophic and focal group was only marginally significant.

**Drug-resistant epilepsy according to the ILAE commission**

Recently the ILAE proposed the following definition for drug-resistant epilepsy (Kwan et al., 2010): failure of adequate trials of two tolerated, appropriately chosen and used AED schedules to achieve sustained seizure freedom. In response to this, and to make our article as up-to-date as possible, we applied this definition to our cohort in addition to our definition at two points in time: at 5 years after enrollment and at last contact.

A comparison of both definitions shows that there is very little difference (**Table 6.3**). The overall conclusion is more or less the same; in both cases intractability or drug-resistance can be temporary, continuing, or delayed. However, the ILAE definition labels more patients as being drug-resistant.

**Table 6.3. Comparison of the proposed ILAE definition of drug resistance and our definition of intractability applied to 413 subjects**

| ILAE definition [95] | | Intractability definition as used in the present study | | Intractability definition applied to the fifth and last year of follow-up | |
|---|---|---|---|---|---|
| Drug resistant at the end of the fifth year of follow-up | 36 (8.7%) | A period of intractability during the first five years of follow-up | 34 (8.2%) | Intractable during the fifth year of follow-up | 18 (4.4%) |
| Drug resistant at last contact | 48 (11.6%) | Intractable during the last year of follow-up | 35 (8.5%) | Intractable during the last year of follow-up | 35 (8.5%) |
| Only drug resistant at the end of the fifth year of follow-up | 12 (2.9%) | Only a period of intractability during the first five years of follow-up | 15 (3.6%) | Only intractable during the fifth year of follow-up | 4 (1.0%) |
| Drug resistant at the end of the fifth year of follow-up and at last contact | 24 (5.8%) | A period of intractability during the first five years of follow-up and in the last year of follow-up | 19 (4.6%) | Intractable during the fifth year and last year of follow-up | 14 (3.4%) |
| Only drug resistant at last contact | 24 (5.8%) | Only intractable during the last year of follow-up | 16 (3.9%) | Only intractable during the last year of follow-up | 16 (3.9%) |

**Table 6.4. Intractability in the first five years as a predictor of intractability in the final year of follow-up depending on the length of the period of intractability during the first five years**

| Length of the period of intractability during the first five years | Intractable in the first five years | Intractable in the final year | Sensitivity % | Specificity % |
|---|---|---|---|---|
| one-year period | 38 | 20 | 57.1 | 95.2 |
| 18-month period | 29 | 15 | 42.9 | 96.3 |
| two-year period | 24 | 13 | 37.1 | 97.1 |
| three-year period | 18 | 11 | 31.4 | 98.1 |

Certainly there is little doubt about treatment failure when a person still has seizures; however, we consider that in terms of severity of epilepsy, the ILAE definition may be too broad in labeling patients with only sporadic seizures as having intractable epilepsy. On the other hand, our definition may not label some highly refractory patients with brief remissions as intractable, when in fact they are. Having used the ILAE definition, we think that it is difficult to apply in a large cohort study, as the history of each individual patient has to be judged carefully, and the intra-observer and inter-observer variability may be high. It should be stressed that it is not our intention to decide which definition is best or to promote our definition. We merely used our definition as a tool to study the course of intractability. In future cohort studies, we advocate the use of one worldwide accepted definition to make comparisons between studies easier. We consider the proposed definition of the ILAE as a good step forward.

**Considerations**

Considering the high proportion of patients with temporary intractability, one could argue that the time span used in our definition of intractability was too short, leading to the inclusion of too many subjects not fundamentally intractable. **Table 6.4** shows our attempt to predict intractability in the final year of the 15-year follow-up with intractability in the first 5 years, while varying the period of continuous seizures. However, a longer period of continuous seizures in the first 5 years led to a decreased sensitivity of the prediction, whereas specificity remained almost the same. In this case, fewer subjects being intractable in the final year of follow-up would have been identified. Consequently, a longer period of continuous seizures as part of the definition of intractability does not solve the problem. Moreover, of the 14 patients with intractability lasting 4–5 years, two reached a 5-year and two a 1-year terminal remission. Therefore, determining how long a patient has to have frequent seizures to be labeled intractable remains arbitrary.

Apart from the time span in our definition of intractability, using only two AEDs could be a matter of discussion. Other investigators use or recommend three AEDs (Camfield & Camfield, 1996; Kwong et al., 2003; Malik et al., 2008), although there is ample evidence that a third AED has little or no effect (Arts et al., 2004; Mohanraj & Brodie, 2006). Moreover, all patients who were intractable in the final year and 31 of the 34 patients with early onset had used at least three AEDs during follow-up. Considering this, we think that the number of AEDs in our definition is not an issue.

Furthermore, there might be discussion about subjects in our study having an intractable seizure pattern in the last year of follow-up while using only one AED. After a long period of intractability, it may be best for a patient to stop medication or to reduce polytherapy in case none of the therapies is really effective. Many physicians would probably have labeled these subjects as being intractable;

however, in the present study we applied our definition strictly, and by doing so may have underreported the occurrence of intractability.

The course of intractability was studied during a period of impressive maturation of the child's brain. The fact that many patients had temporary intractability might be the result of these processes. On the other hand, the phenomenon of late-onset intractability might result from a continuing process of epileptogenesis.

We studied the course of intractability using an objective approach and did not address the subjective severity of intractability, although we realize that this is also important, especially for patients just reaching adulthood.

In this study, incorrect diagnoses of intractability may have been made as a result of noncompliance, incorrect medication, or incorrect diagnosis or classification of epilepsy.

We attempted to exclude these errors to the best of our ability. During the first 5 years, regular plasma concentrations of AEDs were taken, giving us an impression of compliance. We did not have this information for the patients in the last year of follow-up, unless it was indicated in their medical records. The Dutch Study of Epilepsy in Children was a pragmatic study, conducted with experienced physicians working according to their usual clinical practice.

To our knowledge, only a few cohort studies on childhood-onset epilepsy have aimed to identify possible reasons (other than clinical features) for the onset or ending of intractability, which makes the present study uncommon. Only a few studies reported that remission after intractability and relapse occurred in conjunction with changes in medication (Luciano & Shorvon, 2007; Callaghan et al., 2011; Choi et al., 2011). Although this is a delicate topic we think that the success or failure of treatment has to be considered at all times in future research investigating intractability.

The fact that we found no risk factors for temporary, continuing, or late-onset intractability might be due to the small numbers, even though our cohort is one of the largest with childhood-onset epilepsy. Only meta-analyses using multiple cohorts might be able to detect these risk factors.

## CONCLUSIONS

At least 12% of patients with childhood-onset epilepsy will have a period of intractability during a 15-year follow-up. Onset, course, and duration of intractability can fluctuate to a great extent, and periods of remission and intractability can alternate with each other. Intractability can be temporary (especially in case of early onset), but can also begin many years after diagnosis, and in that case, is more likely to persist. These findings are in line with other investigations.

Apart from the risk factors for intractability, it is difficult to predict the time of onset of intractability and whether it will be temporary. Due to the relatively low frequency of intractability, meta-analyses are almost certainly needed for this.

This study did not find a clear explanation for the variation in intractability. The most probable explanation is the natural course of the epilepsy itself, as intractability developed in some despite an early and successful start of treatment, and in only 16% could medication be held responsible for the termination or late onset of intractability. However, the effect of medication may be different in patients who did not have a period of intractability. More research is needed on the actual role of AEDs on the process of epileptogenesis; the question remains whether AEDs modify this process or merely refine it.

Despite recent reports by the ILAE commission, a solid and all-encompassing definition of intractability, also taking into account the severity of sporadically occurring seizures, remains to be established.

## ACKNOWLEDGMENTS

This work was financially supported by the Dutch National Epilepsy Fund [grant number 05-06]. They had no role in the design and conduct of the study, data collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## DISCLOSURE

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**REFERENCES**


Abou-Khalil BW. (2007) Is epilepsy intractability predetermined or acquired? Epilepsy Curr 7:9–10.

Altunbasak S, Herguner O, Burgut HR. (2007) Risk factors predicting refractoriness in epileptic children with partial seizures. J Child Neurol 22:195–199.

Arts WF, Geerts AT, Brouwer OF, Peters AC, Stroink H, Van Donselaar CA. (1999) The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood. Epilepsia 40:726–734.

Arts WF, Brouwer OF, Peters AC, Stroink H, Peeters EA, Schmitz PI, Van Donselaar CA, Geerts AT. (2004) Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 127:1774–1784.

Berg AT. (2004) Understanding the delay before epilepsy surgery: who develops intractable focal epilepsy and when? CNS Spectr 9:136–144.

Berg AT, Levy SR, Novotny EJ, Shinnar S. (1996) Predictors of intractable epilepsy in childhood: a case–control study. Epilepsia 37:24–30.

Berg AT, Langfitt J, Shinnar S, Vickrey BG, Sperling MR, Walczak T, Bazil C, Pacia SV, Spencer SS. (2003) How long does it take for partial epilepsy to become intractable? Neurology 60:186–190.

Berg AT, Lin J, Ebrahimi N, Testa FM, Levy SR, Shinnar S. (2004) Modeling remission and relapse in pediatric epilepsy: application of a Markov process. Epilepsy Res 60:31–40.

Berg AT, Vickrey BG, Testa FM, Levy SR, Shinnar S, Dimario F, Smith S. (2006) How long does it take for epilepsy to become intractable? A prospective investigation. Ann Neurol 60:73–79.

Berg AT, Levy SR, Testa FM, D'Souza R. (2009) Remission of epilepsy after two drug failures in children: a prospective study. Ann Neurol 65:510–519.

Bouma PA, Peters AC, Brouwer OF. (2002) Long term course of childhood epilepsy following relapse after antiepileptic drug withdrawal. J Neurol Neurosurg Psychiatry 72:507–510.

Brown I, Sheeran P, Reuber M. (2009) Enhancing antiepileptic drug adherence: a randomized controlled trial. Epilepsy Behav 16:634–639.

Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. (2007) Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 62:382–389.

Callaghan B, Schlesinger M, Rodemer W, Pollard J, Hesdorffer D, Allen Hauser W, French J. (2011) Remission and relapse in a drug-resistant epilepsy population followed prospectively. Epilepsia 52:619–626.

Camfield PR, Camfield CS. (1996) Antiepileptic drug therapy: when is epilepsy truly intractable? Epilepsia 37(Suppl. 1):S60–S65.

Casetta I, Granieri E, Monetti VC, Gilli G, Tola MR, Paolino E, Govoni V, Iezzi E. (1999) Early predictors of intractability in childhood epilepsy: a community-based case–control study in Copparo, Italy. Acta Neurol Scand 99:329–333.

Choi H, Heiman G, Pandis D, Cantero J, Resor SR, Gilliam FG, Hauser WA. (2008) Seizure remission and relapse in adults with intractable epilepsy: a cohort study. Epilepsia 49:1440–1445.

Choi H, Heiman GA, Munger Clary H, Etienne M, Resor SR, Hauser WA. (2011) Seizure remission in adults with long-standing intractable epilepsy: an extended follow-up. Epilepsy Res 93:115–119.

Gastaut H. (1969) Classification of the epilepsies. Proposal for an international classification. Epilepsia 10(Suppl.):14–21.

Geerts A, Arts WF, Stroink H, Peeters E, Brouwer O, Peters B, Laan L, Van Donselaar C. (2010) Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch study of epilepsy in childhood. Epilepsia 51:1189–1197.

Huttenlocher PR, Hapke RJ. (1990) A follow-up study of intractable seizures in childhood. Ann Neurol 28:699–705.

ILAE. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 22:489–501.

ILAE. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 30:389–399.

ILAE. (1993) Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy. Epilepsia 34:592–596.

Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, Moshe SL, Perucca E, Wiebe S, French J. (2010) Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 51:1069–1077.

Kwong KL, Sung WY, Wong SN, So KT. (2003) Early predictors of medical intractability in childhood epilepsy. Pediatr Neurol 29:46–52.

Loscher W, Schmidt D. (2006) Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. Epilepsia 47:1253–1284.

Luciano AL, Shorvon SD. (2007) Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. Ann Neurol 62:375–381.

Malik MA, Hamid MH, Ahmed TM, Ali Q. (2008) Predictors of intractable childhood epilepsy. J Coll Physicians Surg Pak 18:158–162.

Mohanraj R, Brodie MJ. (2006) Diagnosing refractory epilepsy: response to sequential treatment schedules. Eur J Neurol 13:277–282.

Sabaté E. (2003) Adherence to long-term therapies: evidence for action. World Health Organization, Geneva.

Schmidt D, Loscher W. (2005) Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. Acta Neurol Scand 111:291–300.

Sillanpää M, Schmidt D. (2006a) Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain 129:617–624.

Sillanpää M, Schmidt D. (2006b) Prognosis of seizure recurrence after stopping antiepileptic drugs in seizure-free patients: a long-term population-based study of childhood-onset epilepsy. Epilepsy Behav 8:713–719.

Takenaka J, Aso K, Watanabe K, Okumura A, Negoro T. (2000) Transient seizure remission in intractable localization-related epilepsy. Pediatr Neurol 23:328–331.

Vervloet M, Van Dijk L, Santen-Reestman J, Van Vlijmen B, Bouvy ML, De Bakker DH. (2011) Improving medication adherence in diabetes type 2 patients through real time medication monitoring: a randomized controlled trial to evaluate the effect of monitoring patients' medication use combined with short message service (SMS) reminders. BMC Health Serv Res 11:5.

**SUPPORTING INFORMATION**

Additional Supporting Information may be found in the online version of this article and in **Appendix 5**:

**Table S1**. Course of epilepsy and effect of treatment for 15 patients with temporary intractability.

**Table S2**. Course of 16 patients with late-onset intractability.

# Chapter 7 General discussion

The main objective of this thesis was to study the course and long-term outcome of childhood-onset epilepsy. Our hospital-based study with prospective follow-up since the time of diagnosis may not have been the most ideal approach. A population-based study would have been preferred to better describe the accurate incidence of childhood-onset epilepsy and all its different epilepsy types and syndromes, but such a study is very expensive and both time and labor consuming. Moreover, in practice, most patients contact their general practitioner after a seizure and are referred to the hospital for further medical examinations, or are brought to the ER of the nearest hospital right away. We might have missed subjects with minor seizures who were treated by their general practitioner and those that did not seek medical help at all. This might have biased our study to patients with more severe epilepsy. However, in view of the low proportion of remote symptomatic etiology in our cohort and the estimated 75% recruitment rate, this possible bias does not seem to be so bad. What is more, this study did have several advantages (most of them discussed in the former chapters) that must be taken into account, in particular the size of the cohort and the length of follow-up. We think that, despite several disadvantages, the present study did enhance the knowledge of childhood-onset epilepsy.

Before discussing the main results, a remark has to be made about the terms ‘long-term’ and ‘outcome’. The word outcome suggests a final condition. This is mostly not the case in epilepsy as there is enough evidence by now that a patient’s condition can alter as time goes on. Patients in remission for many years, for example, can get recurrent seizures and they even can become intractable. On the other hand, patients with monthly seizures for years can reach remission, sometimes even for a long time. Our study as well as some other studies demonstrated this [17, 83]. The word ‘long-term’ is rather arbitrary, but as there have been no studies so far with a life-long follow-up of patients with epilepsy, all studies with a follow-up exceeding the ones that have been published up to now give more insight into the course and ‘present state’ of patients at a further point in time. Our follow-up was on average 15 years since the time of diagnosis. Most other cohort studies had a shorter duration of follow-up. Only a few studies had a longer follow-up, however, all of them had fewer patients [21, 24, 28, 29, 96], and not all had a prospective follow-up from the time of diagnosis [21, 29]. With these remarks in mind the reader should realize that our results are only a snapshot at a certain point in time during the life of our patients.

In the next paragraphs, I will discuss the various outcome measures that were used in the previous chapters and will put them into a broader perspective.

Outcome in terms of terminal remission and intractability.

We studied the outcome of our cohort in terms of terminal remission at three points in time: at two, five and ~15 years after enrollment. At two years, 57% of the patients had a terminal remission of at least one year, at five years even a larger proportion (i.e. 64%) had a terminal remission of at least two years, and at 15 years the proportion of patients with a terminal remission of at least five years was as high as 71%. These results show a promising development of childhood-onset epilepsy over the years. Even more promising is the fact that of the 413 subjects with a 15-year follow-up, 24% had seizures only during the first year of follow-up and were in remission since then. This is 22% of the 466 patients of the original cohort we first published about.

Another promising development is that the percentage of patients still having seizures in the 'last' year of follow-up declined from 43% at two years, to 24% at five years, and to 19% at ~15 years. However, a drawback was the increase in the number of patients with intractability, defined as having no remission exceeding three months during a minimum period of one year of observation despite adequate treatment. In the second year 4.5% (21/466) was intractable, in the fifth year 6% (27/453), and in the final year 8.5% (35/413). Based on these results, we conclude that with lengthier follow-up fewer patients will continue having seizures, but there is a small increasing group of patients whose epilepsy deteriorates and ends in intractability. Only 8 of the 35 patients being intractable in the final year of follow-up had probably been intractable since the early years of follow-up, which is 2% of the 413 subjects with an extended follow-up.

In practice, what do these results mean for a physician and his patient with newly diagnosed epilepsy? Overall, chance of a good outcome is high as shown in the previous paragraph, but this will not be the case for every single patient. In this study and in many other studies, several variables proved to be associated with outcome. The most mentioned and strongest predictors were without doubt etiology and type of epilepsy as was demonstrated in our study as well (**Figure 7.1** and **Figure 7.2**). These two variables are highly correlated. Patients with idiopathic etiology have the best prospects, while those with remote symptomatic etiology have the worst. In more detail, all patients with idiopathic partial epilepsy eventually will reach a terminal remission of at least five years within 10 years of follow-up versus about 40% of the patients with cryptogenic and/or symptomatic generalized epilepsy (West syndrome, Lennox Gastaut syndrome, epilepsy with myoclonic-astatic seizures of myoclonic absences).

**Figure 7.1: A 5-year terminal remission as a function of etiology and time.**

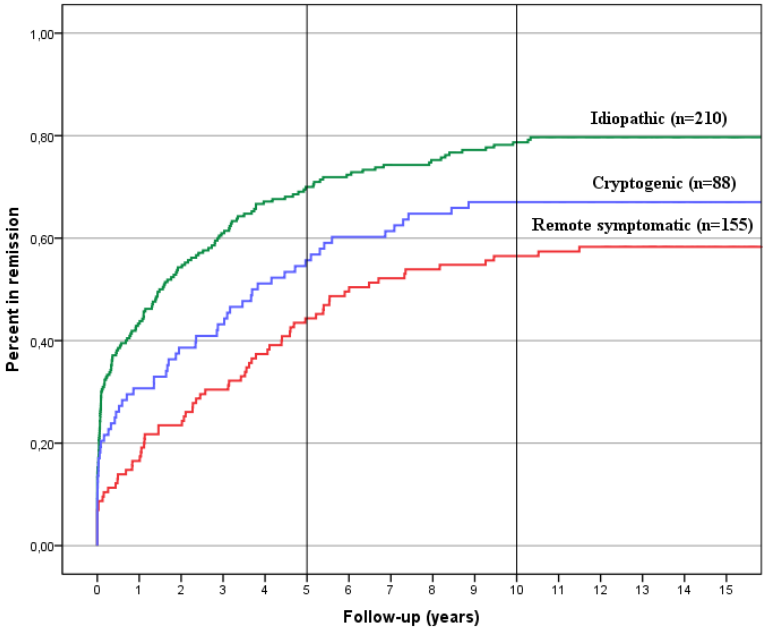
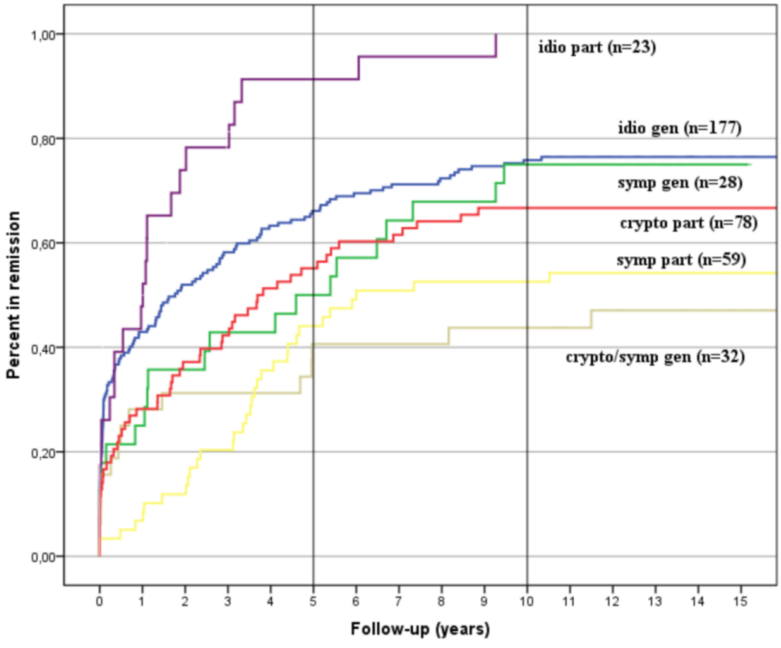



**Figure 7.2: A 5-year terminal remission as a function of epilepsy type and time.**



Although these two variables are each separately significant predictors of final outcome, a combination of variables should predict outcome even better. For this reason, we developed models to predict outcome based on intake information only or on a combination of this information with that of the first six months of follow-up. The models predicting a two-year outcome had a somewhat disappointing sensitivity and specificity (**Table 7.1**), with one of every three patients having an incorrect prediction. These two prognostic models have been tested in a newly recruited cohort of patients [93]. We concluded from that study that although both models predict outcome better than chance, they are insufficiently accurate to be of practical value. Both models performed less well with the validation cohort than with the original cohort, but in both instances the model based on intake and 6-month variables was more accurate.
Compared with the models predicting a two-year outcome, those predicting a five-year outcome had similar sensitivities and specificities and did not predict outcome any better (**Table 7.1**).

In addition to the previous chapters, we here present a model predicting the outcome of the extended follow-up (~15 years). A quick stepwise backward logistic regression analysis predicting a terminal remission of less than one year, showed that type of epilepsy in combination with febrile seizures before intake gave the best results, although specificity was very low in this model. Using intake and 6-month variables, which resulted in a model with a combination of age at onset, type of epilepsy, febrile seizures before intake and terminal remission at six months, hardly did result in a better predictive model. Sensitivity was higher but specificity was the same as in the model with only intake variables.

**Table 7.1 Results of stepwise backward logistic regression analyses predicting terminal remission**

| Predicted outcome | Based on | Probability cutoff % | Sensitivity % | Specificity % | Correct predict % | Area under the ROC curve |
|---|---|---|---|---|---|---|
| $TR_2$ < 6 months | Intake variables only | 38 | 62 | 69 | 67 | 0.69 (poor) |
| | Intake & 6-month variables | 34 | 73 | 73 | 73 | 0.78 (fair) |
| $TR_5$ < 1 year | Intake variables only | 25 | 65 | 64 | 64 | 0.70 (fair) |
| | Intake & 6-month variables | 21 | 69 | 71 | 70 | 0.77 (fair) |
| $TR_E$ < 1 year | Intake variables only | 18 | 73 | 56 | 59 | 0.68 (poor) |
| | Intake & 6-month variables | 16 | 85 | 55 | 61 | 0.74 (fair) |

$TR_2$, $TR_5$, $TR_E$: terminal remission at two or five years after enrollment and after extended follow-up.

Studying these results, it is evident that the accuracy of the prediction models above is not perfect. The area under the ROC curve is a popular test to measure the accuracy of a model. However, this test may not be optimal in models that predict risk for a certain event or to classify subjects [97]. Nonetheless, the results we found were at best fair. It seems that outcome after a mean follow-up of about 15 years is not easier to predict on the basis of intake and 6-month variables than the earlier outcomes. This may be due to the fluctuating course of epilepsy during follow-up. Only subjects with idiopathic partial epilepsy had a steady course, with all having a terminal remission of at least five years. Further, information collected during a longer follow-up period probably better predicts long-term outcome. In a Finnish study, for instance, variables collected during the first year of follow-up were used to predict outcome after a 40-year median follow-up [20]. Having weekly seizures during the first year of follow-up was a strong predictor for drug resistant epilepsy in that study.

The terminal remission at two years and five years after enrollment was measured at fixed points in time, whereas the terminal remission at the end of the extended follow-up was not: subjects had varying lengths of follow-up. Taking the time that passes until the outcome into account, shows that beside the two variables chosen in the logistic regression analysis one additional variable (age at onset) was selected using a Cox proportional hazard model based on only intake variables, with a higher chance of a terminal remission < 1 year at older age (**Table 7.2**). The model based on intake and 6-month variables (**Table 7.3)** also included one additional variable (type of seizure). For these two models no area under the ROC was calculated.

**Tables 7.2 Variables in the Cox proportional hazard model based on intake variables only predicting a 1-year terminal remission during a follow-up of about 15 years.**

| | B | SE | Wald | df | Sig. | Exp(B) * | 95% CI Exp(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Age at onset | -,032 | ,014 | 5,14 | 1 | ,023 | ,969 | ,942 | ,996 |
| Type of epilepsy: | | | 56,64 | 6 | ,000 | | | |
| Symp gen / idiop gen | -,266 | ,220 | 1,46 | 1 | ,227 | ,766 | ,497 | 1,180 |
| Crypto and symp gen / idiop gen | -1,027 | ,252 | 16,53 | 1 | ,000 | ,358 | ,218 | ,588 |
| Idiop part / idiop gen | ,663 | ,228 | 8,49 | 1 | ,004 | 1,941 | 1,243 | 3,033 |
| Symp part / idiop gen | -,796 | ,182 | 19,08 | 1 | ,000 | ,451 | ,316 | ,645 |
| Crypto part / idiop gen | -,435 | ,154 | 8,00 | 1 | ,005 | ,647 | ,479 | ,875 |
| Other / idiop gen | ,542 | ,264 | 4,21 | 1 | ,040 | 1,719 | 1,025 | 2,883 |
| Febrile seizures / no febrile seizures | -,432 | ,207 | 4,36 | 1 | ,037 | ,649 | ,433 | ,974 |

* (Exp(B) < 1: higher chance of a terminal remission < 1 year).

**Table 7.3 Variables in the Cox proportional hazard model based on intake & 6-month variables predicting a 1-year terminal remission during a follow-up of about 15 years.**

| | B | SE | Wald | df | Sig. | Exp(B) * | 95% CI Exp(B) Lower | 95% CI Exp(B) Upper |
|---|---|---|---|---|---|---|---|---|
| Age at onset | -,045 | ,015 | 8,95 | 1 | ,003 | ,956 | ,929 | ,985 |
| Type of seizures: | | | 11,38 | 4 | ,023 | | | |
| CPS / mainly TCS | -,254 | ,213 | 1,42 | 1 | ,233 | ,776 | ,511 | 1,177 |
| SPS / mainly TCS | -,351 | ,298 | 1,39 | 1 | ,238 | ,704 | ,393 | 1,261 |
| Absences / mainly TCS | ,449 | ,172 | 6,80 | 1 | ,009 | 1,567 | 1,118 | 2,198 |
| Other / mainly TCS | -,133 | ,226 | ,35 | 1 | ,557 | ,875 | ,562 | 1,364 |
| Type of epilepsy: | | | 37,91 | 6 | ,000 | | | |
| Symp gen / idiop gen | -,148 | ,222 | ,45 | 1 | ,504 | ,862 | ,558 | 1,332 |
| Crypto and symp gen / idiop gen | -,611 | ,301 | 4,14 | 1 | ,042 | ,543 | ,301 | ,978 |
| Idiop part / idiop gen | ,940 | ,258 | 13,27 | 1 | ,000 | 2,559 | 1,543 | 4,243 |
| Symp part / idiop gen | -,596 | ,190 | 9,81 | 1 | ,002 | ,551 | ,380 | ,800 |
| Crypto part / idiop gen | -,270 | ,161 | 2,80 | 1 | ,094 | ,763 | ,556 | 1,048 |
| Other / idiop gen | ,404 | ,274 | 2,18 | 1 | ,140 | 1,498 | ,875 | 2,564 |
| Febrile seizures / no feb seizures | -,375 | ,209 | 3,20 | 1 | ,074 | ,687 | ,456 | 1,036 |
| Terminal remission 6-month follow-up | ,005 | ,001 | 31,81 | 1 | ,000 | 1,005 | 1,003 | 1,006 |

* (Exp(B) < 1: higher chance of a terminal remission < 1 year).

Beside the modeling efforts above, we have evaluated the accuracy of two newly developed models predicting outcome in collaboration with the Dalhousie University and the IWK Health Centre of Halifax, Nova Scotia, Canada [50]. These two statistical models were based on stepwise logistic regression and on classification tree modeling techniques and were developed using the Canadian and Dutch cohort of children with epilepsy and were cross-validated. The conclusion from that study was that based on currently available clinical and EEG variables, predicting the outcome of childhood epilepsy is difficult and appears to be incorrect in about one of every three patients.

Other prognostic models in epilepsy research were developed but all had moderate to fair results [13, 98-100]. Only one prognostic model constructed to predict the two-year outcome of temporal lobe epilepsy had good results with an accuracy of 0.93, but in a later study the accuracy levels were below 0.80, which the investigators regarded as not being clinically useful [98, 99].

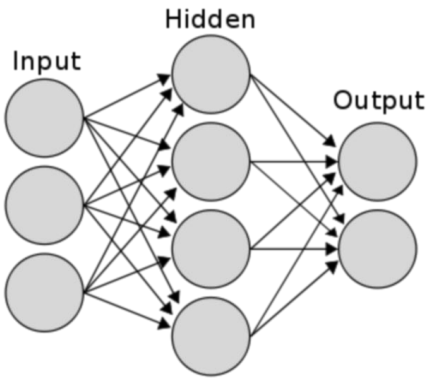
Based on the above findings we have to conclude that the modeling techniques above are not of sufficient quality to make accurate predictions. However, it might be that we and other investigators still have not been able to identify accurate predictors for the outcome of epilepsy. Perhaps, new or refined imaging techniques, the finding of biomarkers in blood or cerebrospinal fluid, or altered gene expressions might provide these. Nevertheless, the diversity of epilepsy types, syndromes and etiology and the fact that patients with the same phenotype or genotype often have different

outcomes makes it uncertain if prediction of outcome in patients with epilepsy using multivariate analysis techniques will be more accurate in future than it is at present.

Other modeling techniques have been explored and developed. The need for these is obvious. In a review about computer modeling in epilepsy the following was stated: '*Epilepsy is a complex set of disorders that can involve many areas of cortex as well as underlying deep brain systems. The myriad manifestations of seizures, as varied as déjà vu and olfactory hallucination, can thereby give researchers insights into regional functions and relations. Epilepsy is also complex genetically and pathophysiologically, involving microscopic (ion channels, synaptic proteins), macroscopic (brain trauma and rewiring) and intermediate changes in a complex interplay of causality. It has long been recognized that computer modeling will be required to disentangle causality, to better understand seizure spread and to understand and eventually predict treatment efficacy' [101]*.

Artificial neural network models, for instance, are non-linear statistical data modeling or decision making tools that can be used to model complex relationships between inputs and outputs or to find patterns in data (**Figure 7.3**).

**Figure 7.3 Simplified view of a neural network**




One study had the objective to model successful outcomes after epilepsy surgery using this technique [102]. The investigators stated that standard multivariate techniques with the same goal had an accuracy of only 75-80%. With neural network models, they were able to predict seizure outcome with an accuracy of more than 95%. In an earlier study, accuracy results of 82% and 95% were found in an attempt to select patients for epilepsy surgery [103]. Using discriminant functions on the same patient sample gave much lower accuracies (55% and73%). Another study predicted

outcome of epilepsy with a 91% correct prediction rate [104]. Other applications of this technique in the field of epilepsy were the classification of subgroups of primary generalized epilepsy based on parameters obtained from EEG signals, and the outcome of drug treatment based on genetic markers [105, 106]. Berg et al. used Markov modeling to determine the probability that a patient with epilepsy will be in remission at a certain point in time during a median 7-year follow-up [71]. With this technique, which is a special application of the neural networks modeling technique, they were able to differentiate the fluctuating course of epilepsy for various epilepsy types to a certain extent. At present, more research in the field of epilepsy is being done using the above techniques. The Global Research in Pediatrics is a network of excellence (Grip) with the main aim to stimulate and facilitate the development and safe use of medicine in children, as drug development programs are usually only applicable to adults. One of the aims is to achieve a scientific consensus on: the role of pharmacokinetic/ pharmacodynamics (PK/PD) modeling in pediatric drug development to be proposed at the regulatory level, the use of simulation to reduce the number of children enrolled in trials and the number of samples for lab tests, and how the extrapolation methodology can be used in regulatory procedures. The data of the Dutch study of epilepsy in children will be used in this project.

Although the artificial network modeling technique looks promising and has many advantages, there are also disadvantages (**Table 7.4**). It is for example difficult to understand the exact nature of the relationship between each single input variable and the predicted outcome, which makes it not possible to determine which variables are the strongest predictors of outcome. The output of neural network models is more difficult to interpret than that of the traditional multivariate techniques. With neural networks one can get an accurate prediction, while with the traditional techniques more insight into the problem can be obtained. Furthermore, there are no practical guidelines for how to select input variables, although in some studies the traditional techniques were used to select the input variables for neural network modeling [103, 104]. Finally, using a model in other datasets is not as easy as using logistic regression analysis: with logistic regression coefficients it is possible to calculate the probability of a certain outcome on a simple calculator, while one will need a copy of the trained software to do the same with the neural network model.
Considering all points mentioned above, we think that models developed to predict course or outcome of epilepsy at present are still not sufficient and accurate enough to be used in daily clinical practice, at least not for a single person.

**Table 7.4 Advantages and disadvantages of using neural networks for predicting medical outcomes [107]**

| |
|---|
| **Advantages** |
| 1. Neural network models require less formal statistical training to develop |
| 2. Neural network models can implicitly detect complex nonlinear relationships between independent and dependent variables |
| 3. Neural network models have the ability to detect all possible interactions between predictor variables |
| 4. Neural networks can be developed using multiple different training algorithms |
| **Disadvantages** |
| 1. Neural networks are a "black box" and have limited ability to explicitly identify possible causal relationships |
| 2. Neural networks models may be more difficult to use in the field |
| 3. Neural network modeling requires greater computational resources |
| 4. Neural network models are prone to overfitting |
| 5. Neural network model development is empirical, and many methodological issues remain to be resolved |

Outcome in terms of mortality

Beside the outcome in terms of terminal remission and intractability, we studied the mortality in our cohort. The results showed that mortality was significantly higher only in those with remote symptomatic etiology and was mainly caused by their underlying condition. This finding was demonstrated by others as well [15, 58, 66, 108, 109]. In this study none of the subjects with idiopathic etiology died. They had the same mortality rate as the Dutch population. A person with idiopathic etiology only has a higher risk of dying during a status epilepticus or as a result of drowning or severe trauma during an epileptic seizure. Further, some patients with epilepsy can get depressed and sometimes become suicidal. Other than this, there is a chance of sudden unexplained death (SUDEP) as a result of epilepsy. The frequency is very low, however, especially in children [110]. In our study the crude rate might have been 3/10,000 person-years of follow-up maximally. Yet, in the long-term follow-up study of Sillanpää much higher and disturbing rates were found: 18 SUDEPs occurred on a total of 8692 years of follow-up, which leads to a crude SUDEP rate of 20.7/10,000 persons-years of follow-up, which is 7 times higher than in our study [111]. Of all deaths in that study, 30% were due to SUDEP of which seven times in case of idiopathic etiology. In our study SUDEP did not occur in subjects with idiopathic etiology. One of the reasons might be that SUDEP in subjects with idiopathic etiology occurs at older age, as was suggested in the Finnish study mentioned above (median age at SUDEP: 27 years; range: 13-48). Regarding this finding and the fact that our cohort was younger at last contact (median age: 20.4; range 12.2–32.5 years),

SUDEP cases have to be expected in our idiopathic etiology group in the next years. Especially those with idiopathic generalized epilepsy using Lamotrigine might have a higher risk [112].

Outcome in case of fast response to medication

In our cohort, about one third of the subjects had a fast response to medication. They had a remission of at least 6 months that began within two months after the start of treatment, and were subsequently randomized to stop treatment or continue treatment for another six months. At two years after randomization the recurrence rates of the 6-month and 12-month treatment groups were similar. Four years after randomization, there still was no significant difference in the recurrence rates, and neither in terminal remission. However, the group with 6-month treatment had relatively more late recurrences during follow-up and had a slightly worse terminal remission. We could not exclude that these findings might have been the result of the early withdrawal of treatment.
Also at the end of the extended follow-up, the terminal remission in both groups was similar: 80% (71% without and 9% with AED at last contact) of the 6-month treatment group had a terminal remission of more than 5 years, versus 75% (64% without and 11% with AED at last contact) in the 12-month group (95% CI of difference: -8.2; 17.7). In the 6-month group one subject with epilepsy as a result of a stroke died nine years later following cardiac arrest. Further, there were no differences in duration of epilepsy (interval between onset and last seizure), number of AEDs used during the first five years of follow-up, number of subjects still on AEDs at last contact, and number of subjects having seizures or being intractable in the last year of follow-up.
Beside the randomized subjects with a fast response to medication, there were an additional 38 subjects in our cohort with a fast response who were not randomized, mostly because parents refused or because of a language barrier. These subjects were treated according to the usual clinical practice, which means that most of them received medication much longer. During the first five years of follow-up all three groups had the same recurrence rate (6-month group: 59%, 12-month group: 51%; non-randomized group: 58%) and the mean number of AEDs used during these five years were similar. When we compare all randomized with the non-randomized fast responders, none of the variables mentioned above differed. Only the mean duration of medication during the first five years of follow-up was significantly longer in the group without randomization, as was to be expected (35.0 versus 25.5 months, ANOVA $F=6.448$, $p=0.01$).
From the findings above we conclude that in children with a fast response to treatment, early withdrawal of medication after a short period of remission may not lead to negative long-term consequences. Several outcome measures at the end of follow-up were similar between randomized and non-randomized fast responders. Despite this, it is possible that there were differences in

seizure frequency or severity, or that recurrences occurred later in time (after more than four years of follow-up), but we did not study these in detail.
The five variables that were predictive of an excellent terminal remission at four years after randomization in multivariate analyses (normal EEG, idiopathic etiology, having only absences, age at onset < 6 years, and no postictal signs) were not all predictive of a good outcome after extended follow-up. EEG and postictal signs did not matter anymore in univariate analysis, but the other variables did. Of the subjects with absences, more than 90% reached a 5-year terminal remission without medication during these years irrespective of age at onset. Subjects with other types of seizures, idiopathic etiology, and onset before the age of six had this outcome in 84% of the cases, and for those with later onset this was true for 61% of the cases (95% CI of difference: 4.2-41.3, $p<0.05$). For those of them with non-idiopathic etiology, these results were 71.4% with onset before six years of age versus 48.1% thereafter (95% CI of difference: 3.5; 43.2, $p<0.1$). Based on these results, subjects with absences are still good candidates for early withdrawal of medication, but subjects with other seizure types, non-idiopathic etiology, and onset after six years of age are not.

Outcome in terms of social economic status

Other than the outcomes described above, there were more aspects of epilepsy that needed attention. Besides the seizures, the AEDs with possible side effects, and the regular visits to hospitals, a patient has to deal with the effect of epilepsy on his or her social situation, educational and occupational achievement, and quality of life. Perhaps these aspects have more impact on subjects with an ordinary life having late onset of seizures than on young children with early onset. The most interesting finding of our study was that subjects with idiopathic etiology were comparable to their Dutch age peers in terms of living arrangements, having a partner or offspring and employment status, but not in terms of educational and occupational achievement. A lower educational attainment was reported by others as well [14, 15, 27, 29, 113] with a similar trend even for those with epilepsy only, normal intelligence and for those in remission and off AEDs. As described earlier, this could be a result of mild impairment of cognitive functions preceding the onset of epilepsy [81, 114-120].
In chapter 5, we reported the age-adjusted standardized incidence rates for subjects with idiopathic etiology and for subjects in remission, but not specifically for subjects with idiopathic etiology having a 5-year terminal remission and in addition being off AEDs at last contact. To show that the lower educational and occupational levels were not a result of active epilepsy and/or ongoing treatment, we here present the standardized incidence rates for this latter group.

**Table 7.5 Age-adjusted standardized incidence rates (SIR) for subjects with idiopathic etiology having a 5-year terminal remission and being off AEDs at last contact** (* p<0.05).

| **Present education (n= 68)** | **SIR (95% CI)** | **Highest attained education (n=67)** | **SIR (95% CI)** | **Occupational level (n=61)** | **SIR (95% CI)** |
|---|---|---|---|---|---|
| Lower vocational, general secondary, pre-university | 1.01 (0.64-1.51) | | | Elementary: jobs with simple duties | 0.44 (0.09-1.27) |
| Intermediate vocational | 1.30 (0.87-1.86) | primary, lower vocational or lower general secondary | 1.27 (0.83-1.86) | Lower: jobs with duties at the level of preliminary vocational education | 1.26 (0.83-1.85) |
| Higher vocational | 0.99 (0.54-1.67) | higher general secondary or pre-university or intermediate vocational | 1.11 (0.77-1.54) | Intermediate: jobs with duties at the level of intermediate vocational education | 1.14 (0.74-1.68) |
| Scientific | 0.25* (0.03-0.92) | higher vocational or scientific | 0.43* (1.16-0.93) | Higher/scientific: jobs with duties at the level of higher vocational or scientific education | 0.63 (0.25-1.30) |

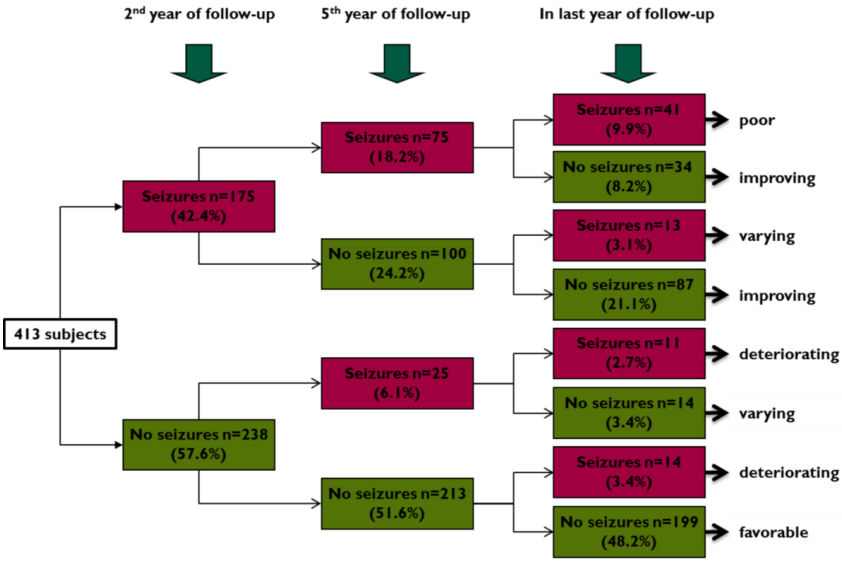
According to **Table 7.5**, fewer students followed a scientific education at last contact and fewer employees than expected attained a higher vocational or scientific education. These significant findings further strengthen the hypothesis that mild impairment of cognitive functions might be found in these subjects. This impairment might have been present before the onset of epilepsy, or developed later due to seizures or AEDs. However, it is possible that 'having epilepsy' was the reason for following education at a slower pace, or at a lower level, even though their cognitive abilities were not impaired. It is even possible that subjects with disorders like this are less ambitious in life, also because of the associated stigma, and are reserved to a certain extent by their fear of new seizures. More research is needed to confirm whether cognitive impairments or any of the above mentioned possible explanations are indeed the basis for the lower educational achievement.

Beside the educational attainment, the marginally significant lower occupational level found in the whole group of subjects with idiopathic etiology was no longer present for those of them in remission and off AEDs, although the rate was still lower than expected. As mentioned before, more research is needed in this field, especially in under-employment.

Course of epilepsy and treatment during follow-up

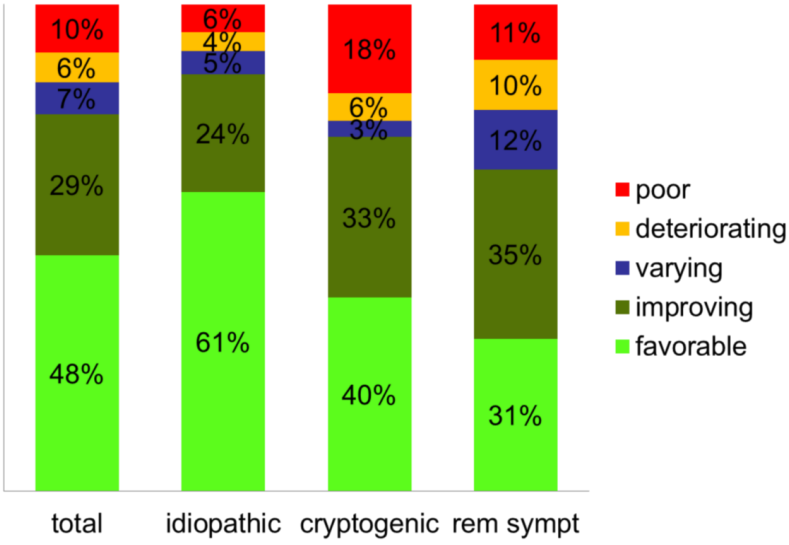
During our study we did not only pay attention to the 'final' outcome of epilepsy, but to the course during follow-up as well. In three selected years of follow-up, we checked if seizures occurred or not (**Figure 7.4**).

**Figure 7.4 Course of epilepsy during follow-up**




Subjects with a favorable, varying or deteriorating course had a change of situation along the years of follow-up (**Figure 7.5**). In the other groups the course seemed to be steadier, at least for the three selected years. We concluded that the course of epilepsy can be inconsistent, and changes may occur after considerable periods of time. We also studied intractability during follow-up and showed a similar pattern: subjects can have early or late onset of intractability. It may be temporary, and sometimes it is interrupted by long periods of remission. Both the course of epilepsy and intractability are strongly dependent on etiology, age, and response to medication or early course during follow-up. One third of our cohort had their final seizure within the first year of treatment, but this group may have had a good outcome anyway, even without taking medication.

**Figure 7.5 Course of epilepsy during follow-up for the cohort and for each etiological group**

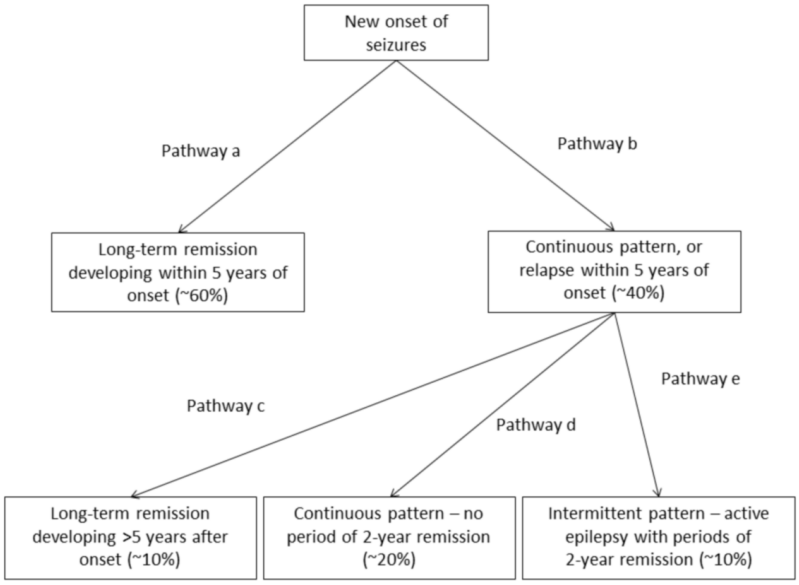



On the other hand, one third of our subjects still used AEDs at last contact, showing the limitation of treatment. We also did not find a large role for treatment in preventing or terminating intractability as was discussed in chapter 6. Therefore, we agree with the statement that AEDs mostly suppress seizures but do not treat the epilepsy itself [121]. Juvenile myoclonic epilepsy may be the best example of this: medication is successful but once it is stopped new seizures mostly occur. In benign cases, childhood-onset epilepsy is a self-limiting disorder and the course is probably only marginally influenced by the treatment given. In other cases, epilepsy deteriorates despite the trials of numerous treatment strategies, and it is far from plausible that bad compliance, drug resistance or tolerance are the only causes for this. As a matter of fact, if drug resistance or tolerance would be autonomic mechanisms not related to the severity of epilepsy, these phenomena would be equal in all epilepsy types. In a recent study of subjects with juvenile myoclonic epilepsy true drug resistance was only found in those with a combination of three seizure types, but not in those with only myoclonic jerks with or without absences [122].

Recently, some investigators proposed a remission and relapse model for the temporal aspects of seizures in epilepsy based on their findings and that of others [123]. Remission was defined as two years without seizures, and with long-term remission they meant a terminal remission of at least two years, instead of the five years we used. They found that of adult subjects with refractory epilepsy (seizures in the past two years, at least five years after onset and who used at least two appropriate

AEDs during that time), 70% had a continuous seizure pattern with no periods of remission and 30% had an intermittent pattern with 2-year remission periods (**Figure 7.6**).
When we apply this model and the 2-year remission definition to our cohort, we found that 234 (56.7%) of our subjects who had a 15-year follow-up (n=413) developed long-term remission within 5 years of onset, which was about similar to what was suggested in the above schedule (pathway a). However, 82 (19.9%) of our subjects reached a terminal remission of at least two years after the first five years of onset (pathway c), which was twice as high as was suggested above.

**Figure 7.6 Remission and relapse model of the temporal aspects of prognosis of epilepsy**

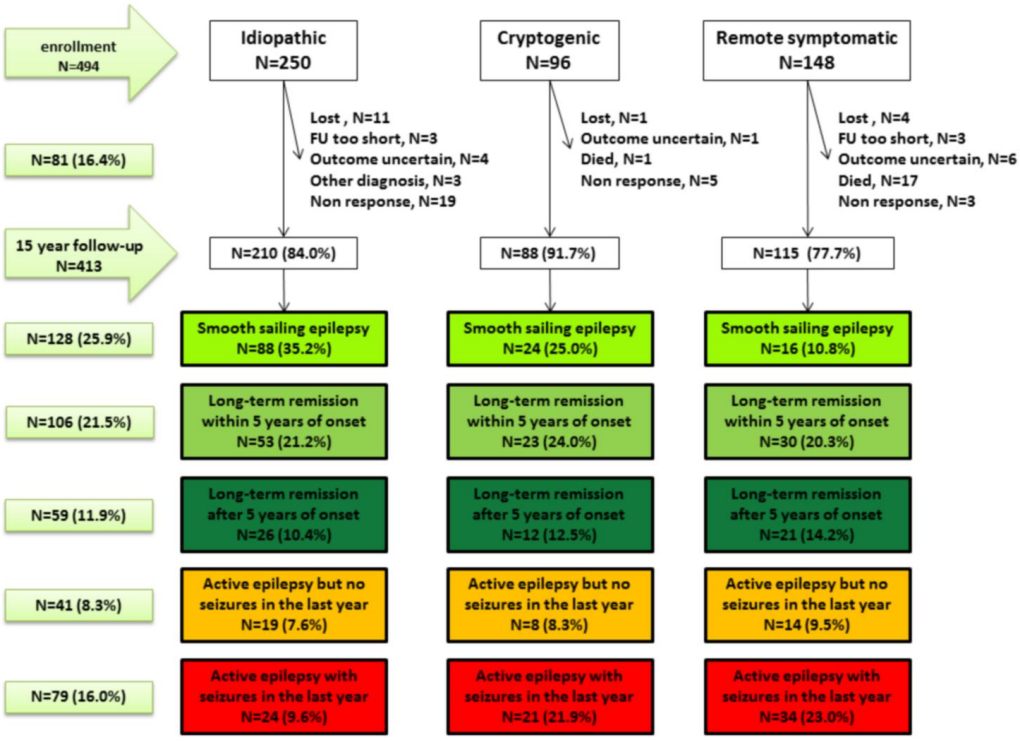



Further, at most 52 (12.6%) had a continuous pattern (pathway d) and at least 45 (10.9%) had an intermittent pattern (pathway e), whereas Neligan et al. found that 20% had a continuous and 10% an intermittent pattern, which means that the proposed model when applied to children is incorrect for the pathways c, d and e. Our continuous pattern group had no 2-year remission periods during the first five years of follow-up, but could have had remission periods after these years. However, accurate information about this later period was not available. In fact, in case of late remissions the continuous pattern group would become smaller than it was and the intermittent group would become larger, which makes the differences between the proposed model and our results even bigger than they are.
Despite these differences in outcome, Neligan et al. concluded that there seems to be considerable heterogeneity in seizure patterns in people who do not enter long-term remission in the early years

after diagnosis. Like us, they found that some people who had a remission in the early years still developed refractory epilepsy, and some subjects with continuous seizures for at least five years entered terminal remission. Also they wondered to what extent the long-term remission developed within five years of onset represented the natural history of benign epilepsy or was a treatment effect. They believe both probably play a role and their clinical experience suggests that for those without remission treatment will often reduce the severity, timing or frequency of seizures in beneficial ways. With this, we fully agree.

In line with the above remission and relapse model we would like to end with the following outcome schedule, in which a separation is made between the three etiological categories to make comparison with other cohorts easier (**Figure 7.7**).

**Figure 7.7 Outcome schedule based on the originally included subjects with epilepsy, with long-term remission meaning a terminal remission of at least five years and active epilepsy meaning having seizures in the last five years of follow-up**



The results of our study suggest that there is a group of subjects with smooth sailing epilepsy, which we have added to this schedule: 82 subjects became seizure free within 2 months of AED-use and remained so during the rest of the 15-year follow-up and 4 subjects had a fast response but had a follow-up of only 5 years. Further, 42 subjects were seizure free within 2 months after enrollment without treatment and stayed free of seizures during follow-up. In total, 128 subjects had smooth sailing epilepsy which is 25.9% of the 494 subjects who were originally included in this study. All percentages in the schedule refer to these subjects. By doing this we will get a more realistic view of the prognosis of newly diagnosed patients with epilepsy. For outcomes per epilepsy type or syndrome we refer to Chapter 4. The figure below shows that while in the remote symptomatic group more subjects died, in the idiopathic etiology group more subjects did not respond to the 'extended follow-up' questionnaire. They probably were in remission and did not wish to be bothered anymore: a reason we sometimes heard from subjects while doing this research. Smooth sailing epilepsy was significantly less often seen in the group with remote symptomatic etiology compared with the other groups and seizures in the last year of follow-up were significantly more frequent in the groups with non-idiopathic etiology. We did not use our intractability definition in this model, as there still is much debate about which definition best describes refractory, drug-resistant, or intractable epilepsy.

Final conclusion

The overall conclusion of this 15-year follow-up study of childhood-onset epilepsy is favorable. Most children with epilepsy have a good or improving course during follow-up, and in one out of every four children it will be 'smooth sailing'. Most also have a good outcome in terms of remission, intractability, and mortality, but with lengthier follow-up there is a small increasing group of patients whose epilepsy deteriorates and ends in intractability.
Mortality was significantly higher only in those with remote symptomatic etiology and was mainly caused by their underlying condition. The frequency of sudden unexplained death as a result of epilepsy (SUDEP) was very low.
The course of epilepsy can be dynamic, and changes may occur after considerable periods of time. This is also true for intractability. This finding might influence our interpretation of the results of prognostic studies, advice to patients, treatment strategies, and timing of referral for surgery.

Multivariate modeling techniques developed to predict course or outcome of epilepsy are at present not accurate enough to be used in daily clinical practice, at least not for a single person, as one of every three patients will be misclassified. In future, neural network models may be a valuable

alternative by simulating the course and outcome of epilepsy and in that way may contribute to drug development programs for children.

The influence of treatment on the course or outcome of epilepsy seems to be minor, especially for subjects having a benign type of epilepsy and who probably will do well even without treatment. At last contact, one third of all patients still used AEDs, although in most of them it was ineffective as they continued to have seizures or were intractable. The most important role of treatment is perhaps the reduction of the severity, timing or frequency of seizures, making life more comfortable for the patient. Further, it might be possible that treatment reduces the time to remission or prolongs the time to intractability, but this assumption is not based on facts.
In children with a fast response to treatment, early withdrawal of medication after a short period of remission may not lead to negative long-term consequences. Especially subjects with absences are good candidates for early withdrawal of medication.

Subjects with idiopathic etiology have the best results and resemble their Dutch age-peers in mortality, health perception, housing, having a partner, offspring, and employment status. Only educational and subsequent levels of occupation are a matter of concern. The disturbing finding that this group might have mild impairment of cognitive functions preceding the onset of epilepsy has to be examined in more detail. Also the presumption of underemployment is a matter of concern. Another point of interest is the possible occurrence of future SUDEPs in our cohort, if the high rates in the Finnish cohort of Sillanpää are accurate. Further, quality of life is an aspect that has not been highlighted in the current study. Beside this, neural networks analyses gain ground and need more data covering a longer follow-up to fine-tune predictive models. The Dutch Study of Epilepsy in Childhood is a solid basis for doing more research in these fields. The fact that there are only a few studies worldwide with prospective follow-up from the time of diagnosis with a considerable length of follow-up should be an important reason for prolonging the follow-up of the current cohort.

## REFERENCES


1. Fisher, R.S., W. van Emde Boas, W. Blume, C. Elger, P. Genton, P. Lee, and J. Engel, Jr., *Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE).* Epilepsia, 2005. **46**(4): p. 470-2.
2. ILAE, *Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy.* Epilepsia, 1989. **30**(4): p. 389-99.
3. Berg, A.T. and I.E. Scheffer, *New concepts in classification of the epilepsies: Entering the 21st century.* Epilepsia, 2011. **52**(6): p. 1058-62.
4. Gommer, A.M. and M.J.J.C. Poos. *Prevalentie, incidentie en sterfte naar leeftijd en geslacht.* Volksgezondheid Toekomst Verkenning, Nationaal Kompas Volksgezondheid [web page] 2010; Available from: http://www.nationaalkompas.nl/gezondheid-en-ziekte/ziekten-en-aandoeningen/zenuwstelsel-en-zintuigen/epilepsie/cijfers-epilepsie-prevalentie-incidentie-en-sterfte-uit-de-vtv-2010/.
5. Johnston, A. and P.E. Smith, *Epilepsy in the elderly.* Expert Rev Neurother, 2010. **10**(12): p. 1899-1910.
6. Elwes, R.D., A.L. Johnson, and E.H. Reynolds, *The course of untreated epilepsy.* Bmj, 1988. **297**(6654): p. 948-50.
7. Jalava, M. and M. Sillanpaa, *Concurrent illnesses in adults with childhood-onset epilepsy: a population-based 35-year follow-up study.* Epilepsia, 1996. **37**(12): p. 1155-63.
8. Jalava, M. and M. Sillanpaa, *Physical activity, health-related fitness, and health experience in adults with childhood-onset epilepsy: a controlled study.* Epilepsia, 1997. **38**(4): p. 424-9.
9. Jalava, M. and M. Sillanpaa, *Reproductive activity and offspring health of young adults with childhood-onset epilepsy: a controlled study.* Epilepsia, 1997. **38**(5): p. 532-40.
10. Jalava, M., M. Sillanpaa, C. Camfield, and P. Camfield, *Social adjustment and competence 35 years after onset of childhood epilepsy: a prospective controlled study.* Epilepsia, 1997. **38**(6): p. 708-15.
11. Sillanpaa, M., *Children with epilepsy as adults: outcome after 30 years of follow-up.* Acta Paediatr Scand Suppl, 1990. **368**: p. 1-78.
12. Sillanpaa, M., *Remission of seizures and predictors of intractability in long-term follow-up.* Epilepsia, 1993. **34**(5): p. 930-6.
13. Sillanpaa, M., P. Camfield, and C. Camfield, *Predicting long-term outcome of childhood epilepsy in Nova Scotia, Canada, and Turku, Finland. Validation of a simple scoring system.* Arch Neurol, 1995. **52**(6): p. 589-92.
14. Sillanpaa, M., L. Haataja, and S. Shinnar, *Perceived impact of childhood-onset epilepsy on quality of life as an adult.* Epilepsia, 2004. **45**(8): p. 971-7.
15. Sillanpaa, M., M. Jalava, O. Kaleva, and S. Shinnar, *Long-term prognosis of seizures with onset in childhood.* N Engl J Med, 1998. **338**(24): p. 1715-22.
16. Sillanpaa, M., M. Jalava, and S. Shinnar, *Epilepsy syndromes in patients with childhood-onset seizures in Finland.* Pediatr Neurol, 1999. **21**(2): p. 533-7.
17. Sillanpaa, M. and D. Schmidt, *Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study.* Brain, 2006. **129**(Pt 3): p. 617-24.
18. Sillanpaa, M. and D. Schmidt, *Prognosis of seizure recurrence after stopping antiepileptic drugs in seizure-free patients: A long-term population-based study of childhood-onset epilepsy.* Epilepsy Behav, 2006. **8**(4): p. 713-9.
19. Sillanpaa, M. and D. Schmidt, *Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy.* Brain, 2008. **131**(Pt 4): p. 938-44.
20. Sillanpaa, M. and D. Schmidt, *Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy.* Brain, 2009. **132**(Pt 4): p. 989-98.

21. Sillanpaa, M. and D. Schmidt, *Long-term employment of adults with childhood-onset epilepsy: a prospective population-based study.* Epilepsia, 2010. **51**(6): p. 1053-60.
22. Sillanpaa, M. and S. Shinnar, *Status epilepticus in a population-based cohort with childhood-onset epilepsy in Finland.* Ann Neurol, 2002. **52**(3): p. 303-10.
23. Sillanpaa, M. and S. Shinnar, *Obtaining a driver's license and seizure relapse in patients with childhood-onset epilepsy.* Neurology, 2005. **64**(4): p. 680-6.
24. Chin, R.F., P.M. Cumberland, S.S. Pujar, C. Peckham, E.M. Ross, and R.C. Scott, *Outcomes of childhood epilepsy at age 33 years: A population-based birth-cohort study.* Epilepsia, 2011. **52**(8): p. 1513-1521.
25. Kurtz, Z., P. Tookey, and E. Ross, *Epilepsy in young people: 23 year follow up of the British national child development study.* BMJ, 1998. **316**(7128): p. 339-42.
26. Ross, E.M., C.S. Peckham, P.B. West, and N.R. Butler, *Epilepsy in childhood: findings from the National Child Development Study.* Br Med J, 1980. **280**(6209): p. 207-10.
27. Kokkonen, J., E.R. Kokkonen, A.L. Saukkonen, and P. Pennanen, *Psychosocial outcome of young adults with epilepsy in childhood.* J Neurol Neurosurg Psychiatry, 1997. **62**(3): p. 265-8.
28. Kokkonen, E.R., J. Kokkonen, and A.L. Saukkonen, *Do neurological disorders in childhood pose a risk for mental health in young adulthood?* Dev Med Child Neurol, 1998. **40**(6): p. 364-8.
29. Wakamoto, H., H. Nagao, M. Hayashi, and T. Morimoto, *Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan.* Brain Dev, 2000. **22**(4): p. 246-55.
30. Casetta, I., E. Granieri, V.C. Monetti, G. Gilli, M.R. Tola, E. Paolino, V. Govoni, and E. Iezzi, *Early predictors of intractability in childhood epilepsy: a community-based case-control study in Copparo, Italy.* Acta Neurol Scand, 1999. **99**(6): p. 329-33.
31. Casetta, I., E. Granieri, V.C. Monetti, M.R. Tola, E. Paolino, S. Malagu, G. Gilli, V. Govoni, and M. Carreras, *Prognosis of childhood epilepsy: a community-based study in Copparo, Italy.* Neuroepidemiology, 1997. **16**(1): p. 22-8.
32. Casetta, I., V.C. Monetti, S. Malagu, E. Paolino, V. Govoni, E. Fainardi, M.R. Tola, and E. Granieri, *Risk factors for cryptogenic and idiopathic partial epilepsy: a community-based case-control study in Copparo, Italy.* Neuroepidemiology, 2002. **21**(5): p. 251-4.
33. Monetti, V.C., E. Granieri, I. Casetta, M.R. Tola, E. Paolino, S. Malagu, V. Govoni, and R. Quatrale, *Risk factors for idiopathic generalized seizures: a population-based case control study in Copparo, Italy.* Epilepsia, 1995. **36**(3): p. 224-9.
34. Stroink, H., O.F. Brouwer, W.F. Arts, A.T. Geerts, A.C. Peters, and C.A. van Donselaar, *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. Dutch study of epilepsy in childhood.* J Neurol Neurosurg Psychiatry, 1998. **64**(5): p. 595-600.
35. Stroink, H., A.T. Geerts, C.A. van Donselaar, A.C. Peters, O.F. Brouwer, E.A. Peeters, and W.F. Arts, *Status epilepticus in children with epilepsy: Dutch study of epilepsy in childhood.* Epilepsia, 2007. **48**(9): p. 1708-15.
36. Stroink, H., R.J. Schimsheimer, A.W. de Weerd, A.T. Geerts, W.F. Arts, E.A. Peeters, O.F. Brouwer, A. Boudewijn Peters, and C.A. van Donselaar, *Interobserver reliability of visual interpretation of electroencephalograms in children with newly diagnosed seizures.* Dev Med Child Neurol, 2006. **48**(5): p. 374-7.
37. Stroink, H., C.A. van Donselaar, A.T. Geerts, A.C. Peters, O.F. Brouwer, and W.F. Arts, *The accuracy of the diagnosis of paroxysmal events in children.* Neurology, 2003. **60**(6): p. 979-82.
38. Stroink, H., C.A. van Donselaar, A.T. Geerts, A.C. Peters, O.F. Brouwer, O. van Nieuwenhuizen, R.F. de Coo, H. Geesink, and W.F. Arts, *Interrater agreement of the diagnosis and classification of a first seizure in childhood. The Dutch Study of Epilepsy in Childhood.* J Neurol Neurosurg Psychiatry, 2004. **75**(2): p. 241-5.

39. Peters, A.C., O.F. Brouwer, A.T. Geerts, W.F. Arts, H. Stroink, and C.A. van Donselaar, *Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy.* Neurology, 1998. **50**(3): p. 724-30.
40. Arts, W.F., O.F. Brouwer, A.C. Peters, H. Stroink, E.A. Peeters, P.I. Schmitz, C.A. van Donselaar, and A.T. Geerts, *Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood.* Brain, 2004. **127**(Pt 8): p. 1774-84.
41. Arts, W.F., A.T. Geerts, O.F. Brouwer, A.C. Peters, H. Stroink, and C.A. van Donselaar, *The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood.* Epilepsia, 1999. **40**(6): p. 726-34.
42. Geerts, A., W.F. Arts, H. Stroink, E. Peeters, O. Brouwer, B. Peters, L. Laan, and C. van Donselaar, *Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood.* Epilepsia, 2010. **51**(7): p. 1189-97.
43. Geerts, A.T., J.M. Niermeijer, A.C. Peters, W.F. Arts, O.F. Brouwer, H. Stroink, E.A. Peeters, and C.A. van Donselaar, *Four-year outcome after early withdrawal of antiepileptic drugs in childhood epilepsy.* Neurology, 2005. **64**(12): p. 2136-8.
44. van Donselaar, C.A., O.F. Brouwer, A.T. Geerts, W.F. Arts, H. Stroink, and A.C. Peters, *Clinical course of untreated tonic-clonic seizures in childhood: prospective, hospital based study.* Bmj, 1997. **314**(7078): p. 401-4.
45. Callenbach, P.M., P.A. Bouma, A.T. Geerts, W.F. Arts, H. Stroink, E.A. Peeters, C.A. van Donselaar, A.C. Peters, and O.F. Brouwer, *Long-term outcome of childhood absence epilepsy: Dutch Study of Epilepsy in Childhood.* Epilepsy Res, 2009. **83**(2-3): p. 249-56.
46. Callenbach, P.M., P.A. Bouma, A.T. Geerts, W.F. Arts, H. Stroink, E.A. Peeters, C.A. van Donselaar, A.C. Peters, and O.F. Brouwer, *Long term outcome of benign childhood epilepsy with centrotemporal spikes: Dutch Study of Epilepsy in Childhood.* Seizure, 2010.
47. Callenbach, P.M., C.M. Jol-Van Der Zijde, A.T. Geerts, W.F. Arts, C.A. Van Donselaar, A.C. Peters, H. Stroink, O.F. Brouwer, and M.J. Van Tol, *Immunoglobulins in children with epilepsy: the Dutch Study of Epilepsy in Childhood.* Clin Exp Immunol, 2003. **132**(1): p. 144-51.
48. Callenbach, P.M., R.G. Westendorp, A.T. Geerts, W.F. Arts, E.A. Peeters, C.A. van Donselaar, A.C. Peters, H. Stroink, and O.F. Brouwer, *Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood.* Pediatrics, 2001. **107**(6): p. 1259-63.
49. Callenbach, P.M., A.T. Geerts, W.F. Arts, C.A. van Donselaar, A.C. Peters, H. Stroink, and O.F. Brouwer, *Familial occurrence of epilepsy in children with newly diagnosed multiple seizures: Dutch Study of Epilepsy in Childhood.* Epilepsia, 1998. **39**(3): p. 331-6.
50. Geelhoed, M., A.O. Boerrigter, P. Camfield, A.T. Geerts, W. Arts, B. Smith, and C. Camfield, *The Accuracy of Outcome Prediction Models for Childhood-onset Epilepsy.* Epilepsia, 2005. **46**(9): p. 1526-32.
51. Middeldorp, C.M., A.T. Geerts, O.F. Brouwer, A.C. Peters, H. Stroink, C.A. van Donselaar, and W.F. Arts, *Nonsymptomatic generalized epilepsy in children younger than six years: excellent prognosis, but classification should be reconsidered after follow-up: the Dutch Study of Epilepsy in Childhood.* Epilepsia, 2002. **43**(7): p. 734-9.
52. Shinnar, S., C. O'Dell, and A.T. Berg, *Distribution of epilepsy syndromes in a cohort of children prospectively monitored from the time of their first unprovoked seizure.* Epilepsia, 1999. **40**(10): p. 1378-83.
53. Al-Twajri, W.A. and M.I. Shevell, *Atypical benign epilepsy of childhood with rolandic spikes: features of a subset requiring more than one medication for seizure control.* J Child Neurol, 2002. **17**(12): p. 901-4.
54. Camfield, C. and P. Camfield, *Preventable and unpreventable causes of childhood-onset epilepsy plus mental retardation.* Pediatrics, 2007. **120**(1): p. e52-5.
55. Camfield, C. and P. Camfield, *Twenty years after childhood-onset symptomatic generalized epilepsy the social outcome is usually dependency or death: a population-based study.* Dev Med Child Neurol, 2008. **50**(11): p. 859-63.

56. Camfield, C., P. Camfield, K. Gordon, B. Smith, and J. Dooley, *Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication.* J Pediatr, 1993. **122**(6): p. 861-8.
57. Camfield, C., P. Camfield, B. Smith, K. Gordon, and J. Dooley, *Biologic factors as predictors of social outcome of epilepsy in intellectually normal children: a population-based study.* J Pediatr, 1993. **122**(6): p. 869-73.
58. Camfield, C.S., P.R. Camfield, and P.J. Veugelers, *Death in children with epilepsy: a population-based study.* Lancet, 2002. **359**(9321): p. 1891-5.
59. Camfield, P. and C. Camfield, *Epilepsy can be diagnosed when the first two seizures occur on the same day.* Epilepsia, 2000. **41**(9): p. 1230-3.
60. Camfield, P. and C. Camfield, *The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy.* Neurology, 2005. **64**(6): p. 973-5.
61. Camfield, P. and C. Camfield, *Long-term Prognosis for Symptomatic (Secondarily) Generalized Epilepsies: A Population-based Study.* Epilepsia, 2007. **48**(6): p. 1128-32.
62. Camfield, P. and C. Camfield, *Idiopathic generalized epilepsy with generalized tonic-clonic seizures (IGE-GTC): a population-based cohort with >20 year follow up for medical and social outcome.* Epilepsy Behav, 2010. **18**(1-2): p. 61-3.
63. Camfield, P., K. Gordon, C. Camfield, J. Tibbles, J. Dooley, and B. Smith, *EEG results are rarely the same if repeated within six months in childhood epilepsy.* Can J Neurol Sci, 1995. **22**(4): p. 297-300.
64. Camfield, P.R., C.S. Camfield, K. Gordon, and J.M. Dooley, *If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug?* J Pediatr, 1997. **131**(6): p. 821-4.
65. Wirrell, E.C., C.S. Camfield, P.R. Camfield, J.M. Dooley, K.E. Gordon, and B. Smith, *Long-term psychosocial outcome in typical absence epilepsy. Sometimes a wolf in sheeps' clothing.* Arch Pediatr Adolesc Med, 1997. **151**(2): p. 152-8.
66. Brorson, L.O. and L. Wranne, *Long-term prognosis in childhood epilepsy: survival and seizure prognosis.* Epilepsia, 1987. **28**(4): p. 324-30.
67. Berg, A.T. and M.M. Kelly, *Defining intractability: comparisons among published definitions.* Epilepsia, 2006. **47**(2): p. 431-6.
68. Berg, A.T., J.T. Langfitt, F.M. Testa, S.R. Levy, F. DiMario, M. Westerveld, and J. Kulas, *Global cognitive function in children with epilepsy: a community-based study.* Epilepsia, 2008. **49**(4): p. 608-14.
69. Berg, A.T., S.R. Levy, F.M. Testa, and R. D'Souza, *Remission of epilepsy after two drug failures in children: a prospective study.* Ann Neurol, 2009. **65**(5): p. 510-9.
70. Berg, A.T., S.R. Levy, F.M. Testa, and S. Shinnar, *Treatment of newly diagnosed pediatric epilepsy: a community-based study.* Arch Pediatr Adolesc Med, 1999. **153**(12): p. 1267-71.
71. Berg, A.T., J. Lin, N. Ebrahimi, F.M. Testa, S.R. Levy, and S. Shinnar, *Modeling remission and relapse in pediatric epilepsy: application of a Markov process.* Epilepsy Res, 2004. **60**(1): p. 31-40.
72. Berg, A.T., S. Shinnar, W.A. Hauser, M. Alemany, E.D. Shapiro, M.E. Salomon, and E.F. Crain, *A prospective study of recurrent febrile seizures.* N Engl J Med, 1992. **327**(16): p. 1122-7.
73. Berg, A.T., S. Shinnar, S.R. Levy, and F.M. Testa, *Status epilepticus in children with newly diagnosed epilepsy.* Ann Neurol, 1999. **45**(5): p. 618-23.
74. Berg, A.T., S. Shinnar, S.R. Levy, and F.M. Testa, *Newly diagnosed epilepsy in children: presentation at diagnosis.* Epilepsia, 1999. **40**(4): p. 445-52.
75. Berg, A.T., S. Shinnar, S.R. Levy, F.M. Testa, S. Smith-Rapaport, and B. Beckerman, *How well can epilepsy syndromes be identified at diagnosis? A reassessment 2 years after initial diagnosis.* Epilepsia, 2000. **41**(10): p. 1269-75.

76. Berg, A.T., S. Shinnar, S.R. Levy, F.M. Testa, S. Smith-Rapaport, and B. Beckerman, *Early development of intractable epilepsy in children: a prospective study.* Neurology, 2001. **56**(11): p. 1445-52.
77. Berg, A.T., S. Shinnar, S.R. Levy, F.M. Testa, S. Smith-Rapaport, B. Beckerman, and N. Ebrahimi, *Two-year remission and subsequent relapse in children with newly diagnosed epilepsy.* Epilepsia, 2001. **42**(12): p. 1553-62.
78. Berg, A.T., S. Shinnar, S.R. Levy, F.M. Testa, S. Smith-Rapaport, B. Beckerman, and N. Ebrahimi, *Defining early seizure outcomes in pediatric epilepsy: the good, the bad and the in-between.* Epilepsy Res, 2001. **43**(1): p. 75-84.
79. Berg, A.T., S. Shinnar, F.M. Testa, S.R. Levy, D. Frobish, S.N. Smith, and B. Beckerman, *Status epilepticus after the initial diagnosis of epilepsy in children.* Neurology, 2004. **63**(6): p. 1027-34.
80. Berg, A.T., S. Shinnar, F.M. Testa, S.R. Levy, S.N. Smith, and B. Beckerman, *Mortality in childhood-onset epilepsy.* Arch Pediatr Adolesc Med, 2004. **158**(12): p. 1147-52.
81. Berg, A.T., S.N. Smith, D. Frobish, S.R. Levy, F.M. Testa, B. Beckerman, and S. Shinnar, *Special education needs of children with newly diagnosed epilepsy.* Dev Med Child Neurol, 2005. **47**(11): p. 749-53.
82. Berg, A.T., F.M. Testa, and S.R. Levy, *Complete remission in nonsyndromic childhood-onset epilepsy.* Ann Neurol, 2011. **70**(4): p. 566-73.
83. Berg, A.T., B.G. Vickrey, F.M. Testa, S.R. Levy, S. Shinnar, F. DiMario, and S. Smith, *How long does it take for epilepsy to become intractable? A prospective investigation.* Ann Neurol, 2006. **60**(1): p. 73-9.
84. Kwong, K.L., W.K. Chak, S.N. Wong, and K.T. So, *Epidemiology of childhood epilepsy in a cohort of 309 Chinese children.* Pediatr Neurol, 2001. **24**(4): p. 276-82.
85. Kwong, K.L., W.Y. Sung, S.N. Wong, and K.T. So, *Early predictors of medical intractability in childhood epilepsy.* Pediatr Neurol, 2003. **29**(1): p. 46-52.
86. Oskoui, M., R.I. Webster, X. Zhang, and M.I. Shevell, *Factors predictive of outcome in childhood epilepsy.* J Child Neurol, 2005. **20**(11): p. 898-904.
87. Tang-Wai, R., M. Oskoui, R. Webster, and M. Shevell, *Outcomes in pediatric epilepsy: seeing through the fog.* Pediatr Neurol, 2005. **33**(4): p. 244-50.
88. Wirrell, E.C., B.R. Grossardt, E.L. So, and K.C. Nickels, *A population-based study of long-term outcomes of cryptogenic focal epilepsy in childhood: Cryptogenic epilepsy is probably not symptomatic epilepsy.* Epilepsia, 2011. **52**(4): p. 738-45.
89. Dhamija, R., B.D. Moseley, G.D. Cascino, and E.C. Wirrell, *A population-based study of long-term outcome of epilepsy in childhood with a focal or hemispheric lesion on neuroimaging.* Epilepsia, 2011. **52**(8): p. 1522-6.
90. Wirrell, E.C., B.R. Grossardt, L.C. Wong-Kisiel, and K.C. Nickels, *Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study.* Epilepsy research, 2011. **95**(1-2): p. 110-8.
91. Bouma, P.A., A.C. Peters, R.J. Arts, T. Stijnen, and J. Van Rossum, *Discontinuation of antiepileptic therapy: a prospective study in children.* J Neurol Neurosurg Psychiatry, 1987. **50**(12): p. 1579-83.
92. Shinnar, S., E.P. Vining, E.D. Mellits, B.J. D'Souza, K. Holden, R.A. Baumgardner, and J.M. Freeman, *Discontinuing antiepileptic medication in children with epilepsy after two years without seizures. A prospective study.* N Engl J Med, 1985. **313**(16): p. 976-80.
93. Geerts, A.T., W.F. Arts, O.F. Brouwer, A.C. Peters, E.A. Peeters, H. Stroink, and C.A. van Donselaar, *Validation of two prognostic models predicting outcome at two years after diagnosis in a new cohort of children with epilepsy: the Dutch Study of Epilepsy in Childhood.* Epilepsia, 2006. **47**(6): p. 960-5.
94. ILAE, *Guidelines for epidemiologic studies on epilepsy. Commission on Epidemiology and Prognosis, International League Against Epilepsy.* Epilepsia, 1993. **34**(4): p. 592-6.

95. Kwan, P., A. Arzimanoglou, A.T. Berg, M.J. Brodie, W. Allen Hauser, G. Mathern, S.L. Moshe, E. Perucca, S. Wiebe, and J. French, *Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies.* Epilepsia, 2010. **51**(6): p. 1069-77.
96. Casetta, I., M. Pugliatti, R. Faggioli, E. Cesnik, V. Simioni, D. Bencivelli, L. De Carlo, and E. Granieri, *Incidence of childhood and adolescence epilepsy: a community-based prospective study in the province of Ferrara and in Copparo, Italy, 1996-2005.* Eur J Neurol, 2011.
97. Cook, N.R., *Use and misuse of the receiver operating characteristic curve in risk prediction.* Circulation, 2007. **115(**7): p. 928-35.
98. Dlugos, D.J. and R.J. Buono, *Predicting outcome of initial treatment with carbamazepine in childhood focal epilepsy.* Pediatric neurology, 2004. **30**(5): p. 311-5.
99. Dlugos, D.J., M.D. Sammel, B.L. Strom, and J.T. Farrar, *Response to first drug trial predicts outcome in childhood temporal lobe epilepsy.* Neurology, 2001. **57**(12): p. 2259-64.
100. Uijl, S.G., F.S. Leijten, J.B. Arends, J. Parra, A.C. van Huffelen, and K.G. Moons, *Prognosis after temporal lobe epilepsy surgery: the value of combining predictors.* Epilepsia, 2008. **49**(8): p. 1317-23.
101. Lytton, W.W., *Computer modelling of epilepsy.* Nature reviews. Neuroscience, 2008. **9**(8): p. 626-37.
102. Arle, J.E., K. Perrine, O. Devinsky, and W.K. Doyle, *Neural network analysis of preoperative variables and outcome in epilepsy surgery.* Journal of neurosurgery, 1999. **90**(6): p. 998-1004.
103. Grigsby, J., R.E. Kramer, J.L. Schneiders, J.R. Gates, and W. Brewster Smith, *Predicting outcome of anterior temporal lobectomy using simulated neural networks.* Epilepsia, 1998. **39**(1): p. 61-6.
104. Aslan, K., H. Bozdemir, C. Sahin, and S. Noyan Ogulata, *Can neural network able to estimate the prognosis of epilepsy patients according to risk factors?* Journal of medical systems, 2010. **34**(4): p. 541-50.
105. Ogulata, S.N., C. Sahin, and R. Erol, *Neural network-based computer-aided diagnosis in classification of primary generalized epilepsy by EEG signals.* Journal of medical systems, 2009. **33**(2): p. 107-12.
106. Petrovski, S., C.E. Szoeke, L.J. Sheffield, W. D'Souza, R.M. Huggins, and J. O'Brien T, *Multi-SNP pharmacogenomic classifier is superior to single-SNP models for predicting drug outcome in complex diseases.* Pharmacogenetics and genomics, 2009. **19**(2): p. 147-52.
107. Tu, J.V., *Advantages and disadvantages of using artificial neural networks versus logistic regression for predicting medical outcomes.* Journal of clinical epidemiology, 1996. **49**(11): p. 1225-31.
108. Annegers, J.F., W.A. Hauser, and L.R. Elveback, *Remission of seizures and relapse in patients with epilepsy.* Epilepsia, 1979. **20**(6): p. 729-37.
109. Lhatoo, S.D., A.L. Johnson, D.M. Goodridge, B.K. MacDonald, J.W. Sander, and S.D. Shorvon, *Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort.* Ann Neurol, 2001. **49**(3): p. 336-44.
110. Tomson, T., L. Nashef, and P. Ryvlin, *Sudden unexpected death in epilepsy: current knowledge and future directions.* Lancet neurology, 2008. **7**(11): p. 1021-31.
111. Sillanpaa, M. and S. Shinnar, *Long-term mortality in childhood-onset epilepsy.* The New England journal of medicine, 2010. **363**(26): p. 2522-9.
112. Hesdorffer, D.C., T. Tomson, E. Benn, J.W. Sander, L. Nilsson, Y. Langan, T.S. Walczak, E. Beghi, M.J. Brodie, and A. Hauser, *Combined analysis of risk factors for SUDEP.* Epilepsia, 2011. **52**(6): p. 1150-9.
113. Koponen, A., U. Seppala, K. Eriksson, P. Nieminen, A. Uutela, M. Sillanpaa, L. Hyvarinen, and R. Kalviainen, *Social functioning and psychological well-being of 347 young adults*

*with epilepsy only--population-based, controlled study from Finland.* Epilepsia, 2007. **48**(5): p. 907-12.
114. Schouten, A., K. Oostrom, A. Jennekens-Schinkel, and A.C. Peters, *School career of children is at risk before diagnosis of epilepsy only.* Dev Med Child Neurol, 2001. **43**(8): p. 575-6.
115. Oostrom, K.J., A. Smeets-Schouten, C.L. Kruitwagen, A.C. Peters, and A. Jennekens-Schinkel, *Not only a matter of epilepsy: early problems of cognition and behavior in children with "epilepsy only"--a prospective, longitudinal, controlled study starting at diagnosis.* Pediatrics, 2003. **112**(6 Pt 1): p. 1338-44.
116. Henkin, Y., M. Sadeh, S. Kivity, E. Shabtai, L. Kishon-Rabin, and N. Gadoth, *Cognitive function in idiopathic generalized epilepsy of childhood.* Dev Med Child Neurol, 2005. **47**(2): p. 126-32.
117. Vinayan, K.P., V. Biji, and S.V. Thomas, *Educational problems with underlying neuropsychological impairment are common in children with Benign Epilepsy of Childhood with Centrotemporal Spikes (BECTS).* Seizure, 2005. **14**(3): p. 207-12.
118. Beghi, M., E. Beghi, C.M. Cornaggia, and G. Gobbi, *Idiopathic generalized epilepsies of adolescence.* Epilepsia, 2006. **47 Suppl 2**: p. 107-10.
119. Hermann, B., J. Jones, K. Dabbs, C.A. Allen, R. Sheth, J. Fine, A. McMillan, and M. Seidenberg, *The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy.* Brain, 2007. **130**(Pt 12): p. 3135-48.
120. Taylor, J., R. Kolamunnage-Dona, A.G. Marson, P.E. Smith, A.P. Aldenkamp, and G.A. Baker, *Patients with epilepsy: cognitively compromised before the start of antiepileptic drug treatment?* Epilepsia, 2010. **51**(1): p. 48-56.
121. Shinnar, S. and A.T. Berg, *Does antiepileptic drug therapy alter the prognosis of childhood seizures and prevent the development of chronic epilepsy?* Semin Pediatr Neurol, 1994. **1**(2): p. 111-7.
122. Gelisse, P., P. Genton, P. Thomas, M. Rey, J.C. Samuelian, and C. Dravet, *Clinical factors of drug resistance in juvenile myoclonic epilepsy.* Journal of neurology, neurosurgery, and psychiatry, 2001. **70**(2): p. 240-3.
123. Neligan, A., G.S. Bell, J.W. Sander, and S.D. Shorvon, *How refractory is refractory epilepsy? Patterns of relapse and remission in people with refractory epilepsy.* Epilepsy research, 2011. **96**(3): p. 225-30.

## SUMMARY

In this hospital-based study, 494 consecutive children with epilepsy (aged 1 month - 16 years) were prospectively followed up from the time of diagnosis. The main objective of this study was to investigate the course of childhood-onset epilepsy during a period of 15 years and the subsequent outcome in terms of remission, intractability, and mortality. Other points of interest were the early withdrawal of treatment in subjects with a fast response to AEDs, the development of models predicting outcome, and the health and socioeconomic status of subjects with epilepsy. During the first five years, regular visits or contacts were scheduled to ensure detailed gathering of data, such as type and frequency of seizures, etiology, use of antiepileptic drugs and dosage changes, possible side effects, and additional medical examinations. About 15 years after diagnosis a questionnaire was sent to all participants with items not only concerning seizures and medication, but also concerning health perception, restrictions due to epilepsy, other health problems, and in addition social, educational and occupational attainment. In the next section, the content of the chapters describing the results of some of the substudies will be summarized.

Generally in subjects with epilepsy, antiepileptic drugs are withdrawn after a seizure-free period of at least two years. Some subjects have a fast response to treatment and in the past we examined if shorter treatment duration in this group would be possible without increasing the risk of recurrences [39]. In that study subjects with a fast response (having a 6-month remission starting within two months after the beginning of treatment) were randomized, either for a 6- or 12-month treatment. In C**hapter 2** we describe the results of a 4-year follow-up after randomization. During these years, more than half of the 161 children had had one or more recurrent seizures: 59% of the 6-month and 51% of the 12-month group. The difference was not significant. Also the recurrence rates at two years did not differ, but the 6-month group had relatively more late recurrences. After recurrence, 55 children restarted medication of whom 25% without success. Adverse events or death did not occur, except for a status epilepticus after withdrawal in two subjects (one in each group).
Beside the recurrence rate, we studied terminal remission (TR4) and found that 51% of the children had an excellent outcome (TR4 $\geq$ 2 years without AEDs), 21% had a TR4 $\geq$ 2 years with AEDs, and 15% still had seizures in the last year. Differences between the two groups were not significant.
We identified several variables that were predictive of an excellent outcome and based on some of these, we developed a model to identify children who may benefit from early withdrawal. The model correctly classified 73% of the children and was considered fair.
We conclude that there was no significant difference in outcome between the two treatment groups, although the results of the 6-month group were not as good as that of the 12-month group. The

excellent outcome in half of all children meant that unnecessary treatment was prevented for more than one year. Conversely, in some children renewed medication failed, which may be a serious risk of early withdrawal. We cannot recommend early withdrawal in all fast responding children, but our predictive model might be of help.

In **Chapter 3** we described the course and prognosis of childhood-onset epilepsy during the first five years of follow-up. A 1-year terminal remission was found in 76% of the 453 subjects. It was remarkable that 14% of the cohort was completely seizure free since enrollment, and another 27% came into terminal remission within the first year of follow-up. On the other hand, 6% was intractable in the last year, of which half had been intractable in the second year as well. Treatment was used by 86% of the cohort, with half of them using only one AED during follow-up. The proportion of subjects with seizures in the fifth year depended strongly on the number of AEDs used, with an increase following more treatment regimens. However, 60% of the subjects using more than one AED did reach remission in the last year. At final contact, 36% of the cohort still used treatment.
Half of the subjects had a good course with no seizures during the 2nd and 5th year. One quarter had an improving course, with seizures in the 2nd year but not in the 5th year, 6% had a deteriorating course with no seizures in the 2nd year but seizures in the 5th year and 17% had a poor course with seizures in both years. These four groups differed significantly in intake and 6-month variables. Rolandic epilepsy and idiopathic generalized epilepsy had the best course during follow-up and symptomatic or cryptogenic epilepsy the worst.
Based on several significant predictors, two models predicting seizures in the last year were developed: one using intake variables only and one a combination of intake and 6-month variables. The prediction of both models was considered fair, but one of every three children was misclassified.
Based on the results above, we concluded that most children with epilepsy had a good or improving course and a good outcome, and only a minority was intractable. This outcome is in line with other studies, despite differences in cohort composition and length of follow-up. Further, we concluded that intractability seems to have a fluctuating course and failure of one or more AEDs strongly predicts poor outcome, but despite this treatment can still be successful.

In **Chapter 4** the course and outcome of childhood-onset epilepsy during a 15-year follow-up was investigated. A questionnaire with items concerning epilepsy was completed by 413 subjects. Of these subjects, 71% had a 5-year terminal remission, most of them without medication at last contact. The others had active epilepsy, and 8.5% of the cohort ended with intractability.

Course was favorable in half of the cohort, and about 30% had an improving course. In both group, more than 80% had a 5-year terminal remission. About 12% had a varying or deteriorating, and 10% a poor course. At least 60% of the subjects with a poor course were intractable in the final year, versus 28% of those with a deteriorating and 15% of those with a varying course.
One third of the cohort had an early good course during the first five years of follow-up, with no or only seizures during the first 6 months. Part of them relapsed and ended with active epilepsy or intractability. For only a few relapses, we found a plausible explanation.
The mean duration of seizure activity was 6.0 years, with 25% of the cohort having seizure activity for less than one year and 25% for more than 12 years.
Treatment was or had been used by 86% of the subjects, with one third having their last seizure within the first year of treatment. Over 60% of the users stopped treatment (mean duration: 3 years), and 38% continued until last contact, with half of them still having seizures in the last year but one quarter having a terminal remission of at least five years. Most of these results were similar to those at five year follow-up.
We found several significant predictors for active epilepsy and intractability. Based on these, we developed a model for final intractability, with an accuracy that was considered good.
During 15-year follow-up, 18 subjects died of whom 9 during the first five years. The standardized mortality rate of subjects with idiopathic or cryptogenic etiology resembled that of Dutch age peers, but for those with remote symptomatic etiology it was 30 times higher. We found no definite cases of sudden unexplained death (SUDEP).
We concluded that the 15-year outcome in childhood-onset epilepsy is favorable for most children, but 9% will end in intractability. Course of epilepsy can be inconsistent, sometimes with delayed improvement or deterioration. Mortality is higher only in case of remote symptomatic etiology, and is probably a consequence of the underlying severe disorder. The natural course of epilepsy probably best explains course and outcome, with some types of epilepsy being short-lived and others having an inherent poor outcome. Treatment probably has a minor role.

**Chapter 5** deals with other aspects of epilepsy. Half of the 413 subjects reported one or more neurologic brain-related morbidities (mostly the cause of their epilepsy) or other impairments and disabilities. One quarter of the cohort was mentally retarded, ranging from mild to severe.
We compared our cohort with age peers of the Dutch population and calculated age-adjusted standardized incidence rates. The health perception of subjects with normal intelligence was worse for those with active epilepsy, especially for those still using medication. In addition, fewer subjects with a non-idiopathic etiology reported a very good health perception.

Restrictions were reported by 14% of the subjects with normal intelligence, mainly by those with active epilepsy. More subjects still using medication reported restrictions than those off medication. The most frequent restrictions were related to performing activities, or learning things because of concentration and memory problems.
The living arrangements of subjects without remote symptomatic etiology and their Dutch age peers were comparable. Those with remote symptomatic etiology lived in an institution or living group for the disabled more often. None of them had children, whereas the other etiology groups resembled their Dutch age peers in having offspring.
Subjects with idiopathic or cryptogenic etiology following education at last contact resembled their Dutch age peers, although in the group with idiopathic etiology higher vocational or scientific education was slightly underrepresented. For those with remote symptomatic etiology the rate of special education was high. Employees in our cohort had a significantly lower educational attainment than expected, even those with idiopathic etiology.
The employment status of subjects with idiopathic or cryptogenic etiology was similar to that of Dutch age peers, but those with remote symptomatic etiology more often depended on state welfare. When only subjects being part of the labor force were considered, similar employment rates were found for all three etiology groups.
Fewer employees with idiopathic etiology had an occupation based on higher education. Subjects with remote symptomatic etiology had more often an elementary job level.
Beside the comparison of the three etiology groups with the Dutch population, we also compared subjects in remission or not with the population. For many of the variables discussed above, the group in remission did worse than expected. This was mostly a result of subjects with remote symptomatic etiology in this group.
Compared with other studies, our study showed better outcome in terms of marriage/cohabitation, or offspring for those with idiopathic etiology, but outcome in terms of health perception and education was similar.
Based on the findings above, we conclude that even after long-term follow-up, childhood-onset epilepsy has a substantial impact on many aspects of life. However, the idiopathic and cryptogenic etiology groups resembled their Dutch age peers, but the educational and occupational achievement of those with idiopathic etiology were lower than expected. This might be due to the epilepsy and seizures, or to an assumed preexisting common cause for the epilepsy and other brain dysfunctions.

In the past, many different words have been used to label patients with persistent seizures not responding to medication, such as intractability, drug-resistance or refractoriness. In our study we used intractability and defined it as having no remission exceeding 3 months during a minimum

period of one year of observation despite an optimal choice and use of at least two AEDs, either alone or in combination. In **Chapter 6** we studied the course of intractability, in an attempt to find explanations for the development, discontinuation, or chronicity of intractability, and to distinguish the natural course of epilepsy from treatment effects. A comparison was made between intractability in the first five years and intractability in the final year. We also compared our definition with the recently proposed ILAE definition for drug resistant epilepsy.

During the 15-year follow-up, at least 12% of the patients had a period of intractability: 8% with onset during the first 5 years of follow-up and 4% with later onset. In the last year of follow-up 8.5% of the patients were intractable.

Risk factors for intractability during the first five years or last year of follow-up were etiology, younger age at first seizure, epilepsy type, mental retardation at enrollment, and febrile convulsions.

We distinguished three groups: 15 subjects with intractability during the first five years only (group A), 19 subjects with intractability during both the first five years and the final year (group B), and 16 subjects with intractability during the final year (group C).

In group A, the majority had no seizures in the last year of follow-up and many even had a 5-year terminal remission. For five patients the end of intractability could be explained by the introduction of new AEDs or by temporal lobectomy.

The majority of group B used treatment during the entire follow-up. None had substantial periods of remission, 50% had daily to monthly seizures, and all were considered to be drug resistant.

More than half of group C had remission during the first five years of follow-up and discontinued treatment, but all had recurrences and restarted treatment; in four of them without success. This was the only possible explanation we found for late onset of intractability. At the end of follow-up, half of group C were drug-resistant for about 3–8 years.

The three groups did not differ in baseline characteristics, indicating that the risk for patients to fall into any of the three groups was similar. However, group B had shorter remission periods during the 5-year follow-up and a significantly longer time to intractability, and thus more were intractable in the fifth year of follow-up. Comparison of group A with the other two groups showed a tendency for a higher proportion of patients developing mental retardation during follow-up.

Both our definition and that of the ILAE showed that time of onset, course, and duration of intractability can differ between subjects with epilepsy. These aspects are hardly predictable, even though intractability itself can be predicted to a certain extent. A poor course during the first five years of follow-up probably increases the chance of final intractability. The natural course of epilepsy probably best explains the variability of intractability and the effect of medication seems to be minor.

## SAMENVATTING

Aan deze studie hebben in totaal 494 kinderen meegedaan nadat bij hen de diagnose epilepsie was gesteld. Hun leeftijd varieerde van 1 maand tot 16 jaar oud. Het belangrijkste doel van deze studie was het bestuderen van het beloop van kinderepilepsie gedurende een periode van 15 jaar en de uiteindelijke prognose. Er werd onder andere vastgesteld of een patiënt aan het einde van de follow-up aanvalsvrij of medicamenteus onbehandelbaar was geworden. Ook werd nagegaan of de sterfte bij kinderen met epilepsie hoger was dan die van hun Nederlandse leeftijdsgenoten. Andere doelstellingen waren het korter behandelen van patiënten die snel aanvalsvrij werden na start van medicatie zonder toename van nadelige gevolgen, het ontwikkelen van modellen voor de voorspelling van de uiteindelijke uitkomst en het vaststellen van de gezondheidstoestand en sociaal economische status van personen met epilepsie. Tenslotte werd het beloop van 'intractabiliteit' bestudeerd met als doel meer inzicht te krijgen in diverse aspecten hiervan. Met intractabiliteit bedoelen we het hebben van aanvallen gedurende minimaal één jaar met aanvalsvrije periodes van hooguit drie maanden in dat jaar ondanks medicatie.
Gedurende de eerste vijf jaar werden regelmatige visites of telefonische contacten gepland om uitgebreid gegevens te kunnen verzamelen, zoals het soort aanvallen en het aantal, de oorzaak van de epilepsie, het gebruik van medicatie (anti-epileptica) en mogelijke bijwerkingen daarvan en verder aanvullend medisch onderzoek. Na de eerste vijf jaar werd de follow-up beëindigd. Ongeveer 15 jaar na diagnose werd opnieuw contact gezocht met de patiënten en werd een vragenlijst verstuurd aan allen die oorspronkelijk vijf jaar lang werden gevolgd. Deze vragenlijst bevatte niet alleen vragen over hun aanvallen en medicatie, maar ook over hun gezondheidservaring, andere gezondheidsproblemen en ziektes, mogelijke beperkingen als gevolg van hun epilepsie en hun sociaal economische status. In de volgende paragrafen worden de resultaten van enkele deelstudies samengevat.

Normaal gesproken wordt bij patiënten met epilepsie na minimaal twee jaar aanvalsvrijheid besloten tot het afbouwen van de gebruikte anti-epileptica. Sommige personen worden snel aanvalsvrij na de start van medicatie (snelle respons). In het verleden hebben we onderzocht of een kortere behandeling bij deze personen mogelijk is zonder een toename van de kans op nieuwe aanvallen [39]. In die studie kreeg de helft van de personen met een snelle respons medicatie gedurende zes maanden en de andere helft gedurende twaalf maanden. De indeling van de personen gebeurde door middel van loting. Met een snelle respons werd een aanvalsvrije periode bedoeld van minimaal zes maanden met een aanvang binnen twee maanden na de start van medicatie. In

**Hoofdstuk 2** beschrijven we de resultaten na een follow-up van vier jaar na loting. Gedurende deze jaren heeft meer dan de helft van de 161 kinderen met een snelle respons één of meerdere nieuwe aanvallen gehad: 59% van de groep met een behandeling van zes maanden en 51% van de groep met een behandeling van twaalf maanden. Het verschil tussen beide groepen was niet significant. Ook de kans op nieuwe aanvallen twee jaar na loting verschilde niet, maar de groep met de kortere behandeling had relatief meer nieuwe aanvallen die later in de tijd optraden. Na een nieuwe aanval hebben 55 kinderen hun medicatie hervat waarvan een kwart met succes: zij werden opnieuw aanvalsvrij. In het cohort traden verder geen bijwerkingen en sterfte op, met uitzondering van twee personen die een aanval kregen die meer dan 30 minuten duurde (status epilepticus) na het stoppen van de medicatie in (één in elke groep).
Naast de kans op nieuwe aanvallen, hebben we de terminale remissie (interval tussen allerlaatste aanval en laatste contact) berekend en vonden dat 51% van de kinderen een terminale remissie had van meer dan twee jaar zonder medicatie, 21% had ook een terminale remissie van meer dan twee jaar maar met medicatie en 15% had nog steeds aanvallen in het laatste jaar. Verschillen tussen de twee groepen waren niet significant. Op basis van enkele voorspellende variabelen hebben we een model ontwikkeld om kinderen te selecteren die voordeel zouden kunnen hebben van een korte behandeling. Het model deelde 73% van de kinderen goed in, wat betekent dat de accuraatheid van het model als redelijk wordt beschouwd.
We concluderen dat er geen significant verschil in uitkomsten bestond tussen de twee groepen van behandeling, maar de resultaten van de groep met een kortere behandeling waren net iets minder goed dan die van de langere behandeling. Wel moet worden opgemerkt dat met de uitstekende uitkomst bij de helft van alle kinderen onnodige behandeling van meer dan één jaar werd voorkomen. Aan de andere kant werden sommige kinderen die na één of meerdere nieuwe aanvallen hun medicatie hervatten niet meer aanvalsvrij. Dit zou eventueel een risico kunnen zijn van een korte behandeling. We kunnen daarom een korte behandeling niet aanbevelen aan alle kinderen die snel reageren op medicatie, maar met behulp van ons voorspellende model kan een betere selectie van kinderen worden gemaakt die korter kunnen worden behandeld.

In **Hoofdstuk 3** is het beloop en de prognose van kinderepilepsie gedurende de eerste vijf jaar van follow-up beschreven. Van de 453 personen met een 5-jaar follow-up bleek 76% aan het eind minimaal één jaar aanvalsvrij te zijn. Het was opvallend dat 14% van de kinderen geen aanvallen meer heeft gehad sinds de diagnose en een andere 27% had alleen aanvallen in het eerste follow-up jaar en was daarna aanvalsvrij. Anderzijds had 6% in het laatste jaar van follow-up epilepsie die medicamenteus onbehandelbaar was. De helft van hen was ook al onbehandelbaar in het tweede jaar van follow-up.

Anti-epileptische medicatie (AEDs) werd gebruikt door 86% van de kinderen. De helft gebruikte slechts één soort anti-epilepticum gedurende de follow-up. Het aantal personen met aanvallen in het vijfde jaar was sterk afhankelijk van het aantal gebruikte AEDs, met een toename in geval van meer medicatie wisselingen. Desondanks had 60% van de personen die meer dan 1 AED gebruikten geen aanvallen meer in het laatste jaar van de 5-jaar follow-up. Bij het laatste contact gebruikte 36% van alle kinderen uit het cohort nog steeds medicatie.
De helft van de kinderen had een goed beloop van hun epilepsie, zonder aanvallen gedurende het tweede en vijfde jaar. Bij een kwart van het cohort trad een verbetering op tijdens de follow-up met aanvallen gedurende het tweede jaar maar niet meer in het vijfde jaar, 6% had een verslechtering met geen aanvallen in het tweede jaar maar wel in het vijfde jaar en 17% had een slecht beloop met aanvallen in beide jaren. Deze vier groepen verschilden significant in variabelen die al bekend waren bij inclusie en in variabelen die gebaseerd waren op de eerste zes maanden follow-up. Rolandische epilepsie en idiopathisch gegeneraliseerde epilepsie hadden het beste beloop gedurende de follow-up en symptomatisch of cryptogene epilepsie het slechtste.
Op basis van enkele significante variabelen werden twee modellen ontwikkeld met als doel aanvallen te voorspellen in het laatste jaar van follow-up: één gebaseerd op variabelen bekend bij aanvang van de studie en één op een combinatie van deze variabelen en variabelen verzameld tijdens de eerste zes maanden van follow-up. Het voorspellende vermogen van beide modellen werd als redelijk beschouwd, hoewel 1 op elke 3 kinderen een foutieve voorspelling kreeg.
Op basis van de bovengenoemde resultaten concluderen we dat de meeste kinderen met epilepsie gedurende de eerste vijf jaar follow-up een goed beloop of een verbetering daarin hebben en een goede uitkomst zonder aanvallen in het laatste jaar. Slechts enkele kinderen eindigen met medicamenteus onbehandelbare epilepsie. Deze resultaten zijn in overeenstemming met andere studies, ondanks verschillen in de samenstelling van de cohorten en de duur van follow-up. Verder concluderen we dat onbehandelbare epilepsie een wisselend beloop kan hebben en dat falen van één of meerdere anti-epileptica een sterke voorspeller is van een slechte prognose, maar dat ondanks het gebruik van meer dan één anti-epilepticum uiteindelijk toch aanvalsvrijheid kan worden bereikt.

In **Hoofdstuk 4** werd het beloop van kinderepilepsie en de uiteindelijke uitkomst na 15 jaar follow-up beschreven. Een vragenlijst over epilepsie werd ingevuld door 413 personen. Daarvan was 71% aan het einde van follow-up minimaal vijf jaar aanvalsvrij, de meesten zonder medicatie bij het laatste contact. De anderen hadden actieve epilepsie en 8.5% eindigde met medicamenteus onbehandelbare epilepsie.
De helft van het cohort had een goed beloop van de epilepsie en ongeveer 30% had een beloop waarbij verbetering optrad tijdens de follow-up. In beide groepen was uiteindelijk meer dan 80%

minimaal vijf jaar aanvalsvrij. Ongeveer 12% had een wisselend of verslechterend beloop en 10% een uitgesproken slecht beloop. Van de laatste groep had minimaal 60% in het laatste jaar van follow-up medicamenteus onbehandelbare epilepsie versus 28% van degenen met een verslechterend beloop en 15% van degenen met een wisselend beloop.
Gedurende de eerste vijf jaren van follow-up had een derde van het cohort geen aanvallen of alleen gedurende de eerste zes maanden. Na die eerste vijf jaren kreeg een deel van hen opnieuw aanvallen en eindigde met actieve of onbehandelbare epilepsie. Voor slechts een aantal van hen vonden we een logische verklaring.
Het gemiddelde interval tussen de eerste en laatste aanval was 6.0 jaar, maar bij 25% van het cohort was dit interval minder dan één jaar en bij nog eens 25% meer dan 12 jaar.
Anti-epileptica werden gebruikt door 86% van alle personen. Een derde van deze personen had hun laatste aanval binnen een jaar na de aanvang van de medicatie. Meer dan 60% van alle gebruikers stopte uiteindelijk met medicatie gedurende de follow-up (gemiddeld na 3 jaar). Daarnaast gebruikte 38% bij het laatste contact nog steeds medicatie. De helft van deze laatste groep had nog steeds aanvallen in het laatste jaar, maar een kwart was al minimaal vijf jaar aanvalsvrij. De meeste van deze resultaten betreffende medicatie waren gelijk aan die na vijf jaar follow-up.
We vonden verschillende significante voorspellers voor actieve epilepsie en onbehandelbare epilepsie. Uitgaande van deze variabelen werd een model gemaakt met als doel het voorspellen van onbehandelbare epilepsie. De accuraatheid van het model werd als goed beschouwd.
Gedurende de 15 jaar follow-up zijn 18 personen overleden, van wie 9 gedurende de eerste vijf jaar. De gestandaardiseerde sterftecijfers van personen met epilepsie zonder een al langer bestaande hersenafwijking waren vergelijkbaar met die van Nederlandse leeftijdsgenoten, maar voor hen met een hersenafwijking waren deze 30 maal hoger. We vonden geen gevallen van ‘sudden unexplained death’ (SUDEP), waarbij iemand met epilepsie plotseling overlijdt en waar geen andere doodsoorzaak wordt vastgesteld.
Op basis van 15 jaar follow-up kan worden geconcludeerd dat kinderepilepsie een gunstig beloop en uitkomst heeft, maar uiteindelijk zal 9% van alle personen eindigen met medicamenteus onbehandelbare epilepsie. Het beloop van epilepsie kan wisselend zijn, vaak met een verbetering en soms een verslechtering op lange termijn. Sterfte is alleen hoger in geval men naast epilepsie een al langer bestaande hersenafwijking heeft (laat symptomatische epilepsie) en is vermoedelijk een gevolg van deze aandoening. Het natuurlijke beloop van epilepsie is waarschijnlijk de beste verklaring voor de gevonden resultaten, met sommige soorten van epilepsie die kort duren en andere soorten die een ‘ingebakken’ slechte prognose hebben. Anti-epileptica hebben waarschijnlijk maar een beperkte invloed op beloop en prognose.

**Hoofdstuk 5** behandelt andere aspecten van epilepsie. De helft van de 413 personen met een follow-up van 15 jaar had te maken met één of meerdere neurologische hersenaandoeningen (meestal de oorzaak van hun epilepsie) of andere beperkingen en handicaps. Een kwart van het cohort was mentaal geretardeerd, variërend van mild tot ernstig.
Het cohort is vergeleken met leeftijdsgenoten van de Nederlandse bevolking en er werden voor leeftijd gestandaardiseerde incidentiecijfers berekend. De algemene gezondheidstoestand van personen met een normale intelligentie werd als slechter ervaren door degenen met actieve epilepsie, vooral door hen die nog medicatie gebruikten. Ook vonden minder personen met een cryptogene of remote symptomatische etiologie (oorzaak van hun epilepsie) dat hun ervaren gezondheid 'zeer goed' was. Met cryptogeen bedoelen we hier dat er waarschijnlijk wel een onderliggende oorzaak voor de epilepsie bestaat maar deze nog niet bekend is en met 'remote symptomatisch (ook wel laat symptomatisch genoemd) bedoelen we dat de epilepsie veroorzaakt is door een al langer bestaande onderliggende structurele hersenafwijking.
Beperkingen werden gerapporteerd door 14% van de personen met een normale intelligentie, vooral door degenen met actieve epilepsie. Personen die nog medicatie gebruikten gaven vaker aan last te hebben van beperkingen dan personen die geen medicatie meer gebruikten. De meest genoemde beperkingen hadden te maken met het bezig zijn met activiteiten of het leervermogen door geheugenproblemen en verminderde concentratie.
De woonsituatie van personen met idiopathische (voornamelijk genetisch bepaalde en leeftijdsafhankelijke epilepsie) of cryptogene etiologie was vergelijkbaar met hun Nederlandse leeftijdsgenoten, terwijl degenen met remote symptomatische etiologie vaker in een verpleeghuis of speciale woongroep woonden. Geen van deze laatste groep had kinderen, maar de idiopathische en cryptogene groep had even vaak kinderen als hun leeftijdsgenoten. Deze bevinding is in tegenspraak met andere studies waarin minder personen met idiopathische etiologie kinderen hadden. Ook bleek uit deze studies dat deze groep minder vaak een partner had, terwijl in onze studie er evenveel personen samenwoonden met een partner als bij hun leeftijdsgenoten.
Personen met idiopathische of cryptogene etiologie die een opleiding volgden bij het laatste contact waren ook vergelijkbaar met hun leeftijdsgenoten, hoewel in de groep met idiopathische etiologie hoger beroepsonderwijs en een universitaire opleiding enigszins ondervertegenwoordigd waren. Voor degenen met remote symptomatische etiologie was het aantal personen dat speciaal onderwijs volgde hoog. Opvallend was dat de werkende personen in ons cohort een significant lager opleidingsniveau hadden dan hun werkende Nederlandse leeftijdsgenoten, zelfs wanneer ze een idiopathische etiologie hadden. Een zelfde resultaat werd ook in andere studies gevonden.
De werksituatie van personen met idiopathische of cryptogene etiologie was vergelijkbaar met die van hun leeftijdsgenoten, maar degenen met remote symptomatische etiologie waren vaker

arbeidsongeschikt. Wanneer we ons beperken tot de beroepsbevolking, dan bleek het percentage dat werkte even groot te zijn in de drie etiologische groepen (idiopathisch, cryptogeen, remote symptomatisch).
Minder werknemers met idiopathische etiologie hadden een beroep dat gebaseerd was op een hogere opleiding en werkenden met een remote symptomatische etiologie hadden vaker een beroep met eenvoudige taken.
Naast de vergelijking van de drie etiologische groepen met de Nederlandse populatie hebben we ook personen die wel of niet in aanvalsvrij waren vergeleken met hun Nederlandse leeftijdsgenoten. Voor veel van de boven besproken variabelen deed de groep met aanvalsvrijheid het slechter dan verwacht. Dit was meestal het gevolg van het feit dat personen met remote symptomatische etiologie onderdeel uitmaakten van deze groep.
Op basis van de gevonden resultaten concluderen we dat epilepsie begonnen in de kindertijd zelfs na vele jaren een substantiële invloed heeft op veel aspecten van het leven. De idiopathische en cryptogene etiologie groepen waren vergelijkbaar met hun Nederlandse leeftijdsgenoten, hoewel het opleidings- en beroepsniveau van hen met idiopathische etiologie lager was dan verwacht. Dit kan het gevolg zijn van de epilepsie en de aanvallen, of van al bestaande geringe onvolkomenheden in de hersenen die zowel tot epilepsie als tot bepaalde verminderde hersenfuncties hebben geleid.

In het verleden zijn veel termen gebruikt voor het labelen van patiënten met aanhoudende aanvallen zonder reactie op medicatie, zoals ‘intractabiliteit’, medicatie-resistente of refractaire epilepsie. In onze studie hebben we de term intractabiliteit gebruikt, waarmee we bedoelen dat iemand ondanks optimaal gebruik van medicatie gedurende minimaal één jaar regelmatig aanvallen houdt zonder noemenswaardige aanvalsvrije periodes (korter dan 3 maanden). In **Hoofdstuk 6** hebben we het beloop van intractabiliteit beschreven gedurende 15 jaar follow-up, in een poging verklaringen te vinden voor het ontstaan, de beëindiging of de aanhoudendheid van intractabiliteit en om onderscheid te maken tussen het natuurlijk beloop van de epilepsie en de invloed van medicatie. Er werd een vergelijking gemaakt tussen intractabiliteit in de eerste vijf jaar en intractabiliteit in het laatste jaar van follow-up. We hebben onze definitie ook vergeleken met de recentelijk voorgestelde ILAE definitie voor medicatie-resistente epilepsie.
Gedurende de 15-jaar follow-up heeft tenminste 12% van de patiënten een periode van intractabiliteit gehad: 8% met een begin gedurende de eerste vijf jaar van follow-up en 4% met een later begin. In het laatste jaar van follow-up had 8.5% intractabiliteit en waarschijnlijk 4% is gedurende de gehele follow-up ‘intractable’ geweest.

Risicofactoren voor intractabiliteit gedurende de eerste vijf jaren of laatste jaar van follow-up waren etiologie, jonge leeftijd bij eerste aanval, epilepsie type, bestaande mentale retardatie en koortsstuipen.
We onderscheidden 3 groepen: 15 personen met een periode van intractabiliteit alléén gedurende de eerste vijf jaar van follow-up (groep A), 19 personen met intractabiliteit gedurende zowel de eerste vijf jaar als in het laatste jaar van follow-up (groep B) en 16 personen met alléén intractabiliteit gedurende het laatste jaar van follow-up (groep C).
De meerderheid van groep A had geen aanvallen in het laatste jaar van follow-up en velen waren uiteindelijk zelfs minimaal vijf jaar aanvalsvrij. Voor vijf personen kan het beëindigen van de intractabiliteit worden verklaard door de introductie van andere anti-epileptica of door een operatie (temporale lobectomie).
De meeste personen uit groep B hebben gedurende de gehele follow-up medicatie gebruikt. Geen van hen had aanzienlijke periodes van aanvalsvrijheid. De helft had dagelijkse tot maandelijkse aanvallen en allen reageerden niet of onvoldoende op medicatie.
Meer dan de helft van groep C had een periode van aanvalsvrijheid gedurende de eerste vijf jaar follow-up en stopte daarom met medicatie. Ze hadden allemaal één of meerdere nieuwe aanvallen en hervatten hun medicatie, maar bij 4 van hen was dit zonder succes: zij bleven aanvallen houden. Dit was de enige mogelijke verklaring die we hebben gevonden voor het late optreden van intractabiliteit. Aan het einde van de follow-up was de helft van groep C medicamenteus onbehandelbaar voor een duur van 3 tot 8 jaar.
De drie groepen verschilden niet in variabelen die bekend waren bij de diagnose, wat aangeeft dat het risico voor patiënten om in één van de drie groepen terecht te komen gelijk was. Groep B had echter kortere aanvalsvrije periodes gedurende de eerste vijf jaar follow-up, maar het duurde significant langer voordat zij hun periode van intractabiliteit hadden. Daardoor waren er meer personen met intractabiliteit in het vijfde jaar van follow-up.
In vergelijking met groep A ontwikkelden meer personen uit beide andere groepen mentale retardatie tijdens follow-up. Dit verschil was bijna significant.
Zowel onze definitie van intractabiliteit als die van de ILAE toonde aan dat de tijd tot aanvang, beloop en duur van intractabiliteit kan verschillen tussen personen met epilepsie. Deze aspecten zijn nauwelijks te voorspellen, ondanks het feit dat het wel of niet krijgen van intractabiliteit wel tot op zekere hoogt kan worden voorspeld.
Een slecht beloop tijdens de eerste vijf jaar van follow-up verhoogt waarschijnlijk de kans op uiteindelijke intractabiliteit. Het natuurlijke beloop van epilepsie verklaart waarschijnlijk het best de variabiliteit in intractabiliteit. Medicatie lijkt slechts een kleine rol te spelen in het voorkómen of beëindigen van intractabiliteit.

## DANKWOORD

Direct na mijn studie las ik in de krant een advertentie van de Erasmus Universiteit van Rotterdam waarin men iemand zocht die de analyses zou willen doen van een tweetal onderzoeken. Eén daarvan was een epilepsieonderzoek bij volwassenen. Aangezien ik net een doctoraal-onderzoek had uitgevoerd bij patiënten met epilepsie in het kader van gezondheidsleer, als onderdeel van mijn studie Humane Voeding, trok deze studie mijn aandacht. Ik werd aangenomen en leerde Cees van Donselaar kennen voor wie ik jaren met heel veel plezier heb gewerkt. Cees is na enkele jaren cum laude op dit onderzoek gepromoveerd. Dankzij zijn enthousiasme is later het kinderepilepsie onderzoek opgezet, samen met de kinderneurologen Willem Frans Arts, Boudewijn Peters, Oebo Brouwer en Hans Stroink. Later kwam daar Els Peeters bij, die als neuroloog het stokje van Willem Frans overnam in de beide deelnemende ziekenhuizen van Den Haag. In de loop der jaren vertrok Cees en nam Willem Frans zijn plaats in als mijn 'baas'. Ook met hem heb ik vele jaren met heel veel plezier gewerkt. Ons onderzoeksteam was zeer enthousiast en bruiste van de ideeën. We hebben jarenlang een hecht team gevormd, met regelmatige vergaderingen, lange discussies en af en toe interessante culturele en culinaire uitstapjes met onze partners. Ik kijk hier met heel veel plezier op terug.

Tijdens mijn eerste sollicitatiegesprek op de Erasmus Universiteit werd mij gevraagd of ik zou willen promoveren. Ik heb toen geantwoord dat ik dat wel zou willen als het automatisch zou voortvloeien uit mijn werk, maar dat mijn kwaliteit van leven daar niet al teveel onder mocht lijden. Echter, van een promotie is al die jaren geen sprake geweest aangezien mijn taak juist was anderen ter zijde te staan tijdens hun promotie. Bovendien had ik die ambitie eigenlijk niet. Een aantal jaren geleden werd het idee geboren dat ik op het nog liggende materiaal van het Zuid-Hollands kinderepilepsie onderzoek zou kunnen promoveren. Ik kende de gegevens immers als mijn broekzak. Na enige aarzeling ben ik begonnen met het schrijven van het eerste artikel. En wie A zegt moet B zeggen! Na lang zwoegen, veel teleurstellingen en tegenslagen is het dan toch eindelijk gelukt dit boekje af te krijgen. Een hele inspanning, maar dat weten degenen die in het zelfde schuitje hebben gezeten als geen ander! Ik moet trouwens opmerken dat er geen grotere anticlimax bestaat dan de acceptatie van een artikel waaraan je zo hard hebt gewerkt. Je verwacht minimaal fanfares in de straat en knallende champagneflessen, maar er gebeurt niets….

Ik wil mijn hoogleraar Willem Frans Arts ontzettend bedanken, die ondanks zijn drukke agenda altijd tijd vond om mijn vele versies van de artikelen grondig door te lezen. We hebben elkaar al die

jaren weinig gezien, maar hadden wel wekelijks contact per e-mail. Wat een uitkomst is dat medium toch! Ook de anderen van het team, vooral Oebo, Cees en Hans, wil ik bedanken voor het becommentariëren van mijn artikelen. Ieder deed dat op zijn eigen manier: de één wilde alles in groter perspectief zien, de ander bekeek het tot in detail. Ook wil ik de leden van de leescommissie, Prof. dr. P. Sillevis Smitt, Prof. dr. H.A. Moll en Prof. dr . P. Boon hartelijk danken voor hun bijdrage aan deze promotie.

In de loop der jaren zijn er meerdere medewerkers geweest die alle gegevens trouw hebben ingevoerd en uiteenlopende secretariële handelingen hebben verricht voor dit onderzoek. Ik wil vooral Mariette Westendorp en Joke Kuijpers bedanken die meerdere jaren altijd vol inzet voor ons in touw zijn geweest en een beetje gezelligheid brachten in die foeilelijke kamers van de medische faculteit. Ook Linda van Leeuwen wil ik hartelijk bedanken voor de laatste loodjes van invoeren nadat Joke is gestopt met werken.

Uiteraard was dit onderzoek niet tot stand gekomen zonder alle kinderen die destijds in de studie werden geïncludeerd. Dank voor hen en hun ouders!

Simone, jou wil ik hartelijk bedanken voor je onbaatzuchtige hulp bij het ontwerpen en vervaardigen van de omslag en bij het leggen van de eerste contacten met de drukker.

Mijn trouwe Peter ben ik enorm dankbaar voor zijn steun en zijn bemoedigende woorden als het weer eens even tegen zat. En natuurlijk voor de glaasjes witte wijn die hij mij ’s avonds laat bracht wanneer ik weer achter mijn bureau zat te zwoegen, met daarbij af en toe een korte massage om mijn verkrampte schouders weer wat soepeler te maken.

Mijn lieve dochter Charlotte wil ik bedanken voor het doorlezen van veel van mijn teksten. Zij kon hier als buitenstaander even een frisse blik op werpen. Wanneer zij het goed vond, durfde ik het met een gerust hart te versturen. Ik ben dan ook gerust en blij dat zij tijdens de verdediging van mijn proefschrift aan mijn zijde zal staan.

Lieve Roderik, ook jij kent zo langzamerhand al heel wat tegenslagen. Maar het doet me goed om te horen en te zien dat je niet opgeeft. Doorzettingsvermogen is het sleutelwoord. Als je dat niet hebt kom je nergens.

‘Mam, wanneer ga je nou promoveren?’ Hoe vaak heb je me die vraag wel niet gesteld. Ja, lieve Sebas, ik ga eindelijk promoveren! Het idee van de omslag is van jou afkomstig. Toen jij 9 jaar oud was heb je een kameleon geverfd die tot voor kort bij ons in de hal heeft gehangen en mij inspireerde, mede omdat jij rond die tijd na een éénmalige epileptische aanval in het ziekenhuis belandde.

Lieve Jeanette, mijn andere paranimfje, ik ken geen trouwere vriendin dan jij. Ondanks het feit dat je in het buitenland woont, hebben we elkaar sinds we 16 jaar waren niet uit het oog verloren. Dank voor je vriendschap!

Als laatste wil ik mijn drie dierbare zussen bedanken, die zo enorm met me hebben meegeleefd tijdens dit proces. Toen ik 10 jaar oud was is mijn vader overleden en heeft mijn moeder nog jarenlang met de nodige hulp onze boerderij voorgezet. Ik wilde graag in Wageningen studeren, maar had ook belangstelling voor een plaatselijk te volgen opleiding tot medisch analist. In mijn directe omgeving vond men echter dat ik, als enig thuiswonend kind, mijn moeder niet in de steek mocht laten. Gelukkig hebben mijn zussen mij enorm aangespoord om toch voor mezelf te kiezen en naar Wageningen te gaan. Wat had mijn leven er totaal anders uitgezien als ik niet hun raad had opgevolgd!

## CURRICULUM VITAE

Ada Geerts is geboren op 29 december 1959 te Hoogeveen. Van 1972 tot 1978 volgde ze het Atheneum-B op het Menso Alting College in Hoogeveen. Daarna vertrok zij naar Wageningen om al daar Humane Voeding te studeren aan de Landbouwuniversiteit, nu beter bekend als Wageningen Universiteit en Research. Haar doctoraal vakken bestonden uit humane voeding, dierfysiologie en gezondheidsleer. Tijdens haar studie heeft ze stage gelopen bij 'the Department of Social and Preventive Medicine' aan de State University of New York te Buffalo, alwaar ze zich verdiepte in darmkanker en mogelijke risicofactoren. In 1985 rondde ze haar studie af.
Mei 1986 trad zij in dienst als wetenschappelijk medewerkster bij het Instituut voor Maatschappelijke Gezondheidszorg en later bij de afdeling Neurologie in het toenmalige Academisch Ziekenhuis Rotterdam (nu Erasmus MC). Bij deze afdelingen was zij werkzaam aan meerdere onderzoeksprojecten, waarbij haar werkzaamheden varieerden van het leveren van een bijdrage aan het ontwerp, de opzet en uitvoering van de onderzoeken, het beheer van patiëntengegevens, het uitvoeren van statistische analyses tot en met het publiceren van de onderzoeksresultaten. Projecten waar ze onder andere aan werkte waren: 'Kinematica van de lumbale wervelkolom' onder leiding van neurochirurg Dr. M.W. Berfelo en 'Kosten en effecten van bevolkingsonderzoek op borstkanker' onder leiding van prof. Dr. P.J. van der Maas. Daarnaast werkte ze vanaf het begin aan een prospectief onderzoek van volwassenen met één epileptisch insult. Dit project stond onder leiding van Dr. C.A. van Donselaar. Naar aanleiding van dit laatste onderzoek is in 1988 het Zuid-Hollands Kinderepilepsie Onderzoek gestart, waarbij meerdere kinderneurologen en onderzoekscentra betrokken waren. Bovengenoemde projecten hebben geleid tot diverse publicaties en promoties. Ook zijn er nog enkele kortdurende medicatie-trials uitgevoerd en is de 'International Study on Strategies of Treatment of Epilepsy in Children' opgezet, waarbij patiënten met een goede prognose in eerste instantie niet werden behandeld met anti-epileptica. De laatste studie is onlangs afgerond en de eerste publicaties hierover zullen in de komende jaren verschijnen.
Ada Geerts is ingeschreven in het Register van Epidemiologen A.

## LIST OF PUBLICATIONS


1. Arts, W.F., A.T. Geerts, O.F. Brouwer, A.C. Boudewyn Peters, H. Stroink, and C.A. van Donselaar, *The early prognosis of epilepsy in childhood: the prediction of a poor outcome. The Dutch study of epilepsy in childhood.* Epilepsia, 1999. 40(6): p. 726-34.
2. Arts, W.F., O.F. Brouwer, A.C. Peters, H. Stroink, E.A. Peeters, P.I. Schmitz, C.A. van Donselaar, and A.T. Geerts, *Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood.* Brain, 2004. 127(Pt 8): p. 1774-84.
3. Arts, W.F. and A.T. Geerts, *When to start drug treatment for childhood epilepsy: the clinical-epidemiological evidence.* Eur J Paediatr Neurol, 2009. 13(2): p. 93-101.
4. Callenbach, P.M., A.T. Geerts, W.F. Arts, C.A. van Donselaar, A.C. Peters, H. Stroink, and O.F. Brouwer, *Familial occurrence of epilepsy in children with newly diagnosed multiple seizures: Dutch Study of Epilepsy in Childhood.* Epilepsia, 1998. 39(3): p. 331-6.
5. Callenbach, P.M., R.G. Westendorp, A.T. Geerts, W.F. Arts, E.A. Peeters, C.A. van Donselaar, A.C. Peters, H. Stroink, and O.F. Brouwer, *Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood.* Pediatrics, 2001. 107(6): p. 1259-63.
6. Callenbach, P.M., C.M. Jol-Van Der Zijde, A.T. Geerts, W.F. Arts, C.A. Van Donselaar, A.C. Peters, H. Stroink, O.F. Brouwer, and M.J. Van Tol, *Immunoglobulins in children with epilepsy: the Dutch Study of Epilepsy in Childhood.* Clin Exp Immunol, 2003. 132(1): p. 144-51.
7. Callenbach, P.M., W.F. Arts, R. ten Houten, P. Augustijn, W.B. Gunning, E.A. Peeters, A.M. Weber, H. Stroink, Y. Geerts, A.T. Geerts, and O.F. Brouwer, *Add-on levetiracetam in children and adolescents with refractory epilepsy: results of an open-label multi-centre study.* Eur J Paediatr Neurol, 2008. 12(4): p. 321-7.
8. Callenbach, P.M., P.A. Bouma, A.T. Geerts, W.F. Arts, H. Stroink, E.A. Peeters, C.A. van Donselaar, A.C. Peters, and O.F. Brouwer, *Long-term outcome of childhood absence epilepsy: Dutch Study of Epilepsy in Childhood.* Epilepsy Res, 2009. 83(2-3): p. 249-56.
9. Callenbach, P.M., P.A. Bouma, A.T. Geerts, W.F. Arts, H. Stroink, E.A. Peeters, C.A. van Donselaar, A.C. Peters, and O.F. Brouwer, *Long term outcome of benign childhood epilepsy with centrotemporal spikes: Dutch Study of Epilepsy in Childhood.* Seizure, 2010. 19(8): p. 501-6.
10. Carpay, J.A., A.W. de Weerd, R.J. Schimsheimer, H. Stroink, O.F. Brouwer, A.C. Peters, C.A. van Donselaar, A.T. Geerts, and W.F. Arts, *The diagnostic yield of a second EEG after partial sleep deprivation: a prospective study in children with newly diagnosed seizures.* Epilepsia, 1997. 38(5): p. 595-9.
11. Carpay, H.A., W.F. Arts, A.T. Geerts, H. Stroink, O.F. Brouwer, A.C. Boudewyn Peters, and C.A. van Donselaar, *Epilepsy in childhood: an audit of clinical practice.* Arch Neurol, 1998. 55(5): p. 668-73.
12. Geelhoed, M., A.O. Boerrigter, P. Camfield, A.T. Geerts, W. Arts, B. Smith, and C. Camfield, *The accuracy of outcome prediction models for childhood-onset epilepsy.* Epilepsia, 2005. 46(9): p. 1526-32.
13. Geerts, A.T., J.M. Niermeijer, A.C. Peters, W.F. Arts, O.F. Brouwer, H. Stroink, E.A. Peeters, and C.A. van Donselaar, *Four-year outcome after early withdrawal of antiepileptic drugs in childhood epilepsy.* Neurology, 2005. 64(12): p. 2136-8.
14. Geerts, A.T., W.F. Arts, O.F. Brouwer, A.C. Peters, E.A. Peeters, H. Stroink, and C.A. van Donselaar, *Validation of two prognostic models predicting outcome at two years after diagnosis in a new cohort of children with epilepsy: the Dutch Study of Epilepsy in Childhood.* Epilepsia, 2006. 47(6): p. 960-5.

15. Geerts, A., W.F. Arts, H. Stroink, E. Peeters, O. Brouwer, B. Peters, L. Laan, and C. van Donselaar, *Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood.* Epilepsia, 2010. 51(7): p. 1189-97.
16. Geerts, A., O. Brouwer, C. van Donselaar, H. Stroink, B. Peters, E. Peeters, and W.F. Arts, *Health perception and socioeconomic status following childhood-onset epilepsy: The Dutch study of epilepsy in childhood.* Epilepsia, 2011. 52(12): p. 2192-2202.
17. Geerts, A., O. Brouwer, H. Stroink, C. van Donselaar, B. Peters, E. Peeters, and W.F. Arts, *Onset of intractability and its course over time: The Dutch study of epilepsy in childhood.* Epilepsia, 2012. 53(4): p. 741-751.
18. Middeldorp, C.M., A.T. Geerts, O.F. Brouwer, A.C. Peters, H. Stroink, C.A. van Donselaar, and W.F. Arts, *Nonsymptomatic generalized epilepsy in children younger than six years: excellent prognosis, but classification should be reconsidered after follow-up: the Dutch Study of Epilepsy in Childhood.* Epilepsia, 2002. 43(7): p. 734-9.
19. Peters, A.C., O.F. Brouwer, A.T. Geerts, W.F. Arts, H. Stroink, and C.A. van Donselaar, *Randomized prospective study of early discontinuation of antiepileptic drugs in children with epilepsy.* Neurology, 1998. 50(3): p. 724-30.
20. Stroink, H., O.F. Brouwer, W.F. Arts, A.T. Geerts, A.C. Peters, and C.A. van Donselaar, *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. Dutch study of epilepsy in childhood.* J Neurol Neurosurg Psychiatry, 1998. 64(5): p. 595-600.
21. Stroink, H., C.A. van Donselaar, A.T. Geerts, A.C. Peters, O.F. Brouwer, and W.F. Arts, *The accuracy of the diagnosis of paroxysmal events in children.* Neurology, 2003. 60(6): p. 979-82.
22. Stroink, H., C.A. van Donselaar, A.T. Geerts, A.C. Peters, O.F. Brouwer, O. van Nieuwenhuizen, R.F. de Coo, H. Geesink, and W.F. Arts, *Interrater agreement of the diagnosis and classification of a first seizure in childhood. The Dutch Study of Epilepsy in Childhood.* J Neurol Neurosurg Psychiatry, 2004. 75(2): p. 241-5.
23. Stroink, H., R.J. Schimsheimer, A.W. de Weerd, A.T. Geerts, W.F. Arts, E.A. Peeters, O.F. Brouwer, A. Boudewijn Peters, and C.A. van Donselaar, *Interobserver reliability of visual interpretation of electroencephalograms in children with newly diagnosed seizures.* Dev Med Child Neurol, 2006. 48(5): p. 374-7.
24. Stroink, H., A.T. Geerts, C.A. van Donselaar, A.C. Peters, O.F. Brouwer, E.A. Peeters, and W.F. Arts, *Status epilepticus in children with epilepsy: Dutch study of epilepsy in childhood.* Epilepsia, 2007. 48(9): p. 1708-15.
25. van Donselaar, C.A., A.T. Geerts, J. Meulstee, J.D. Habbema, and A. Staal, *Reliability of the diagnosis of a first seizure.* Neurology, 1989. 39(2 Pt 1): p. 267-71.
26. van Donselaar, C.A., A.T. Geerts, and R.J. Schimsheimer, *Usefulness of an aura for classification of a first generalized seizure.* Epilepsia, 1990. 31(5): p. 529-35.
27. van Donselaar, C.A., A.T. Geerts, and R.J. Schimsheimer, *Idiopathic first seizure in adult life: who should be treated?* BMJ, 1991. 302(6777): p. 620-3.
28. van Donselaar, C.A., R.J. Schimsheimer, A.T. Geerts, and A.C. Declerck, *Value of the electroencephalogram in adult patients with untreated idiopathic first seizures.* Arch Neurol, 1992. 49(3): p. 231-7.
29. van Donselaar, C.A., O.F. Brouwer, A.T. Geerts, W.F. Arts, H. Stroink, and A.C. Peters, *Clinical course of untreated tonic-clonic seizures in childhood: prospective, hospital based study.* BMJ, 1997. 314(7078): p. 401-4.
30. van der Maas, P.J., H.J. de Koning, B.M. van Ineveld, G.J. van Oortmarssen, J.D. Habbema, K.T. Lubbe, A.T. Geerts, H.J. Collette, A.L. Verbeek, J.H. Hendriks, and J.H.C.L. Hendriks, *The cost-effectiveness of breast cancer screening.* Int J Cancer, 1989. 43(6): p. 1055-60.

31. van Oortmarssen, G.J., J.D. Habbema, P.J. van der Maas, H.J. de Koning, H.J. Collette, A.L. Verbeek, A.T. Geerts, and K.T. Lubbe, *A model for breast cancer screening.* Cancer, 1990. 66(7): p. 1601-12.

## LIST OF OTHER PUBLICATIONS

32. Rutgers MJ, Geerts AT, Jonker D. *Huisarts, Epilepsie, Taakopvatting: Werkelijkheid en Wenselijkheid.* TSG 1984:62 (11):455.
33. Donselaar CA van, Geerts AT, *First seizure in adult life.* Lancet 1988; II: 36. Letter to the editor.
34. Maas PJ van der, Koning HJ de, Ineveld BM van, Oortmarssen GJ van, Habbema JDF, Lubbe JThN, Geerts AT, Collette HJA, Verbeek ALM, Hendriks JHCL, Rombach JJ, *The cost-effectiveness of breast cancer screening.* In: Gutartige und bosartige Brusterkrankungen unter besonderer Beruecksichtigung der Therapie/Mammographie-Screening. Baebler Verlag; Bern, Switzerland, 1991: 84-101.
35. Arts WFM, Van Donselaar CA, Geerts AT, Stroink H, Brouwer OF, and Peters ACB, *Which criteria may be used to evaluate the result of the treatment of epilepsy?* Neuropediatrics 24, 1993, 169. Abstract.
36. Stroink H, Schimsheimer RJ, de Weerd AW, Geerts AT, Arts WF, Peeters EA, Brouwer OF, Peters ACB, and Donselaar CA van, Developmental Medicine & Child Neurology 2006, 48: 1006–1011. Letter to the editor.

**APPENDIX 1**

# Questionnaire Epilepsy Research

Name:

Date of birth:

**SEIZURES:**

1. When did you have your last epileptic seizure?

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

Day Month Year

If you don't know the exact date of the seizure, please indicate below how long ago you had your last seizure.

- More than 5 years ago
- 3 - 5 years ago
- 2 - 3 years ago
- 1 - 2 years ago
- Less than 1 year ago

**MEDICATION:**

2. Do you currently use medication for your epilepsy?

   - No
   - Yes, please continue with question 4

3. When did you stop your medication?

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |

Day Month Year

If you don't know the exact date, please indicate below how long ago you stopped your medication.

- o More than 5 years ago
- o 3 - 5 years ago
- o 2 - 3 years ago
- o 1 - 2 years ago
- o Less than 1 year ago

4. Are you currently being treated by a specialist because of your epilepsy?

   o Yes Name specialist: .....

   Name hospital: .....

   o No When did you have your last appointment?

   | | | | | | | | |
   |---|---|---|---|---|---|---|---|
   | | | | | | | | |

   Day Month Year

   Name doctor / specialist: ……..

   Name hospital: …….

**HEALTH:**

5. How is your general health perception?

   - o Very good
   - o Good
   - o Moderate
   - o Poor
   - o Very poor
   - o Don't know, refuses answer

6. Apart from your epilepsy, do you have one or more long-lasting illnesses, disorders or handicaps?

   - o Yes
   - o No
   - o Don't know, refuses answer

   If yes, please describe:

   .....
   .....

7. To what extent does epilepsy restrict your daily activities **at home**?

    - Strongly restricted
    - Slightly restricted
    - Not restricted
    - Don't know, refuses answer

    In case of restrictions, please describe:

    ……..…
    ……..…

8. To what extent does epilepsy restrict your daily activities **at school or work**?

    - Strongly restricted
    - Slightly restricted
    - Not restricted
    - Don't know, refuses answer

    In case of restrictions, please describe:

    …….. ……
    ……..…

9. To what extent does epilepsy restrict your daily activities during **sports or other leisure activities**, and to what extent does epilepsy restrict **commuting or traveling**?

    - Strongly restricted
    - Slightly restricted
    - Not restricted
    - Don't know, refuses answer

    In case of restrictions, please describe:

    ……
    ……

**SOCIAL ECONOMIC STATUS:**

We would like to know if persons with epilepsy accomplish the same things as persons without epilepsy. That is why we would like to ask some questions about education, occupation etc.

10. What kind of living arrangement do you have?

    - Single
    - Single parent, with one or more kids
    - Cohabiting or married, no kids
    - Cohabiting or married, with one or more kids
    - Living with parents, but older than 18 years
    - Living with parents, but younger than 18 years
    - Part of other household

11. What is your employment status?

    - Employed
    - Unemployed
    - Volunteer
    - Disabled (with welfare pension)
    - Student
    - Housewife / houseman
    - Unknown

12. What was the highest education that you **attained**?

    - Primary school
    - Lower general secondary education
    - Lower vocational education
    - Higher general secondary or pre-university education
    - Intermediate vocational education
    - Higher vocational education
    - Scientific education (university)
    - Unknown
    - Other, please describe: ……

13. At present, do you follow education?

    - Yes, please describe: ……
    - No

14. In case of no education, what is your profession?

……

15. Remarks:

……
……
……
……
……

Date of completion: ☐☐ ☐☐ ☐☐☐☐

Day Month Year

Residence: ……

Signature: ……

**Thank you very much for completing this questionnaire!**

# APPENDIX 2

**Additional Supporting Information belonging to Chapter 2**

Table E-1: Patient and disease characteristics of 154 children with newly diagnosed epilepsy

| | 6-month group N=77 | 12-month group n=77 | Total n=154 | OR for excellent outcome | 95% CI of OR |
|---|---|---|---|---|---|
| Gender: | | | | | |
| Boys | 36 (47%) | 40 (52%) | 76 | 1.00 | |
| Girls | 41 (53%) | 37 (48%) | 78 | 0.56 | 0.29-1.07 |
| Age at onset (y) (mean): | 6.3 (se 0.4) | 6.8 (se 0.5) | 6.5 (se 0.3) | | |
| Less than 6 years | 32 (42%) | 33 (43%) | 65 | 1.00 | |
| 6 years or more | 45 (58%) | 44 (57%) | 89 | 0.47* | 0.24- 0.91 |
| Number of fits before AED: | | | | | |
| 1 or 2 | 24 (31%) | 17 (22%) | 41 | 1.00 | |
| 3, 4 or 5 | 17 (22%) | 24 (31%) | 41 | 2.21 | 0.89-5.49 |
| 6 thu 10 | 6 (8%) | 8 (10%) | 14 | 0.96 | 0.27-3.45 |
| >10 | 30 (39%) | 28 (36%) | 58 | 2.64* | 1.12-6.19 |
| Positive family history: | 10 (13%) | 9 (12%) | 19 | 0.86 | 0.33-2.26 |
| Febrile convulsions : | 12 (16%) | 9 (12%) | 21 | 1.35 | 0.53-3.44 |
| Seizure type before randomization: | | | | | |
| Generalized Tonic Clonic | 52 (68%) | 57 (74%) | 109 | 1.00 | |
| Simple/complex partial | 13 (17%) | 7 (9%) | 20 | 0.61 | 0.23-1.66 |
| Absence seizures | 12 (16%) | 13 (17%) | 25 | 4.55** | 1.53-13.54 |
| Epilepsy type: | | | | | |
| Generalized | 41 (53%) | 48 (62%) | 89 | 1.00 | |
| Localization related | 31 (40%) | 26 (34%) | 57 | 0.21*** | 0.10-0.45 |
| Mixed | 5 (6%) | 3 (4%) | 8 | 0.53 | 0.12-2.31 |
| Etiology: | | | | | |
| Idiopathic | 47 (61%) | 45 (58%) | 92 | 1.00 | |
| Remote symptomatic | 13 (17%) | 14 (18%) | 27 | 0.34* | 0.14-0.86 |
| Cryptogenic | 17 (22%) | 18 (23%) | 35 | 0.23*** | 0.10-0.57 |
| EEG1 (at intake) | | | | | |
| Normal | 13 (17%) | 21 (27%) | 34 | 1.00 | |
| Epileptic | 48 (62%) | 43 (56%) | 91 | 0.33** | 0.14-0.78 |
| otherwise abnormal | 16 (21%) | 13 (17%) | 29 | 0.39 | 0.13-1.14 |
| EEGs at intake (combined): | | | | | |
| Normal | 10 (13%) | 14 (18%) | 24 | 1.00 | |
| Epileptic | 54 (70%) | 53 (69%) | 107 | 0.29* | 0.10-0.82 |
| otherwise abnormal | 13 (17%) | 10 (13%) | 23 | 0.26* | 0.07-0.96 |
| EEG3 (before randomization): | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Normal | 39 (51%) | 46 (60%) | 85 | 1.00 | |
| Epileptic | 21 (27%) | 18 (23%) | 39 | 0.30** | 0.13-0.69 |
| otherwise abnormal | 17 (22%) | 13 (17%) | 30 | 0.67 | 0.29-1.55 |
| Mental retardation: | 7 (9%) | 11 (14%) | 18 | 0.58 | 0.21-1.60 |
| Pre-existing neurological signs: | 3 (4%) | 7 (9%) | 10 | 0.39 | 0.10-1.61 |
| Post-ictal signs: | 9 (12%) | 6 (8%) | 15 | 0.13** | 0.03-0.62 |

Odds ratios (OR) for excellent outcome (TR4 of at least two years without medication).
*p < 0.05, **p < 0.01, ***p < 0.001

**Table E-2: Multivariate analysis: Odds ratios (OR) and their 95% CI's and derived regression coefficients (RC) after shrinkage (0.89) for the model predicting an excellent outcome in childhood epilepsy**

| | OR | 95% CI | RC |
|---|---|---|---|
| Age at onset:<br>0 = less than 6 years<br>1 = 6 years or more | 0.50* | 0.24-1.05 | -0.61 |
| Etiology:<br>0 = idiopathic<br>1 = non-idiopathic | 0.51* | 0.23-1.10 | -0.60 |
| Absence Seizures:<br>0 = no<br>1 = yes | 4.52*** | 1.47-13.93 | 1.34 |
| Postictal signs:<br>0 = no<br>1 = yes | 0.19** | 0.04-0.99 | -1.48 |
| EEGs at intake (combined):<br>0 = normal<br>1 = abnormal | 0.22*** | 0.08-0.66 | -1.33 |
| Constant | | | 1.87 |

Number of observations = 154, number of covariate patterns = 16.
Goodness of fit test: Pearson $\chi^2$ (10) = 7.92, Prob. >$\chi^2$ = 0.6362.
Area under ROC curve = 0.7730.
Risk score Z: (-0.61 age -0.60 etiology +1.34 absences -1.48 postictal signs -1.33 EEGs + 1.87).
*p < 0.1; **p < 0.05; ***p < 0.01.

## APPENDIX 3

**Additional Supporting Information belonging to Chapter 4.**

**Table S1: Significant variables for active epilepsy ($TR_E$ < 5 year) and final intractability, and odds ratios for intractability (OR) for each value as compared with the reference value of that variable**

| | Number | Active epilepsy | Intractable in final year | OR for intractability (95% CI) |
|---|---|---|---|---|
| Overall | 413 | 120 [29.1%] | 35 [8.5%] | |
| Type of epilepsy | | *** | *** | ** |
| - generalized idiopathic | 176 (42.6%) | 41 [23.3%] | 5 [2.8%] | ref |
| - generalized symptomatic | 29 (7.0%) | 8 [27.6%] | 2 [6.9%] | 2.5 (0.5, 13.7) |
| - generalized cryptogenic or symptomatic | 32 (7.7%) | 15 [53.1%] | 10 [31.2%] | 15.5 (4.9, 49.7) |
| - localization-related idiopathic | 23 (5.6%) | 0 | 0 | .00 |
| - localization-related symptomatic | 59 (14.3%) | 27 [45.8%] | 8 [13.6%] | 5.4 (1.7, 17.1) |
| - localization-related cryptogenic | 78 (18.9%) | 26 [33.3%] | 10 [12.8%] | 5.0 (1.7, 15.3) |
| - unclassifiable | 16 (3.9%) | 1 [6.2%] | 0 | .00 |
| Etiology at enrollment | | *** | *** | *** |
| - idiopathic | 210 (50.8%) | 43 [20.5%] | 6 [2.9%] | ref |
| - remote symptomatic | 115 (27.8%) | 48 [41.7%] | 17 [14.8%] | 5.9 (2.3, 15.4) |
| - cryptogenic | 88 (21.3%) | 29 [33.0%] | 12 [13.6%] | 5.4 (1.9, 14.8) |
| Febrile convulsions before enrollment | | n.s. | (p<0.1) | * |
| - no | 371 (89.8%) | 104 [28.0%] | 28 [7.5%] | ref |
| - yes | 42 (10.2%) | 16 [38.1%] | 7 [16.7%] | 2.4 (1.0, 6.0) |
| Number of seizures in first 6 months | | * | * | * |
| - < 25 | 263 (63.7%) | 67 [25.5%] | 16 [6.1%] | ref |
| - > 25 | 150 (36.3%) | 53 [35.3%] | 19 [12.7%] | 2.2 (1.1, 4.5) |

| | | | | |
|---|---|---|---|---|
| 3-Month remission in first 6 months | | *** | *** | *** |
| - no | 112 (27.1%) | 49 [43.8%] | 23 [20.5%] | ref |
| - yes | 301 (72.9%) | 71 [23.6%] | 12 [4.0%] | 0.2 (0.1, 0.3) |
| Fast response to AED | | *** | *** | *** |
| - no | 181 (43.8%) | 82 [45.3%] | 30 [16.6%] | ref |
| - yes | 173 (41.9%) | 33 [19.1%] | 5 [2.9%] | 0.2 (0.1, 0.4) |
| - no AED | 59 (14.3%) | 5 [8.5%] | 0 | 0 |
| TR at 2 years | | *** | *** | *** |
| - > 1 year | 238 (57.6%) | 43 [18.1%] | 6 [2.5%] | ref |
| - < 1 year | 175 (42.4%) | 77 [44.0%] | 29 [16.6%] | 2.8 (1.8, 4.4) |
| TR at 5 years | | *** | *** | *** |
| - > 1 year | 313 (75.8%) | 51 [16.3%] | 5 [1.6%] | ref |
| - < 1 year | 100 (24.2%) | 69 [69.0%] | 30 [30.0%] | 26.4 (9.9, 70.5) |
| Intractable somewhere during first 5 years of FU | | *** | *** | *** |
| - no | 374 (90.6%) | 90 [24.1%] | 15 [4.0%] | ref |
| - yes | 39 (9.4%) | 30 [76.9%] | 20 [51.3%] | 25.2 (11.2, 56.8) |
| Longest remission in first 5 years | | *** | *** | *** |
| (mean in years, 95% CI) | 3.4 (3.2, 3.5) | 2.3 (2.0, 2.6) | 1.3 (0.9, 1.8) | 0.3 (0.2, 0.4) |
| Number of AEDs in first 5 years | | *** | *** | *** |
| (mean, 95% CI) | 1.7 (1.5, 1.8) | 2.5 (2.2, 2.9) | 3.7 (3.0, 4.3) | 1.9 (1.6, 2.3) |

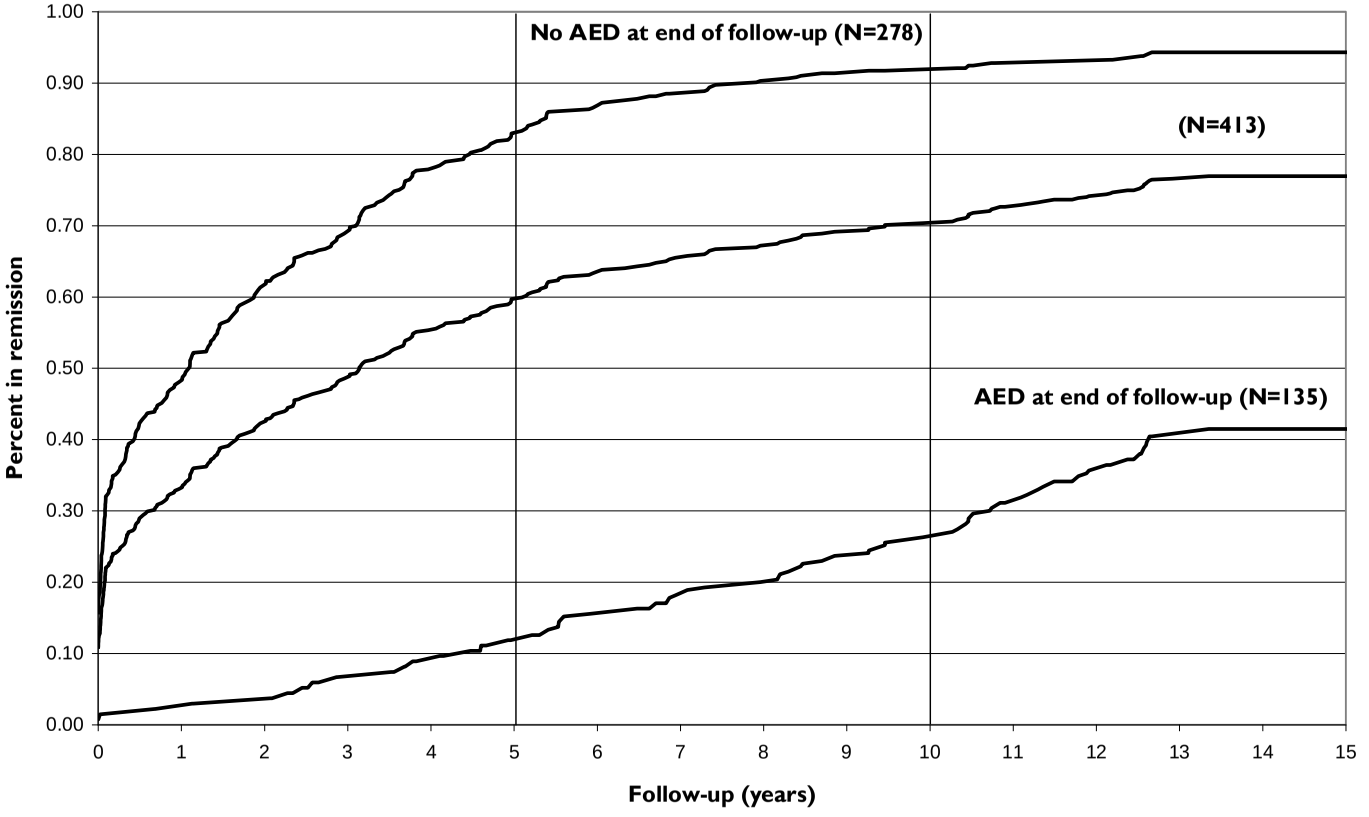
*p < 0.05; **p < 0.001; ***p < 0.0001;
n.s., not significant;
ref, reference for Odds Ratio

**Table S2: Characteristics of nine subjects who died after more than 5 years of follow-up (FU). The causes of death of those who died in the first 5 years have been described in detail previously [48]**

| | | Age (yrs) | FU (yrs) | Etiology | Cause | Mental retardation | Epilepsy type (ILAE) | Cause of death |
|---|---|---|---|---|---|---|---|---|
| 1 | man | 15.7 | 11.2 | Cryptogenic | | IQ 80-100 | Loc rel[1] cryptogenic | Unknown cause, found dead lying on ground. The autopsy report could no longer be obtained. |
| 2 | man | 6.1 | 13.9 | Remote symptomatic | Cerebral palsy | IQ < 70 | Loc rel[1] symptomatic | Stroke as a result of a thrombus in arteria basilaris, followed by bronchopneumonia causing death |
| 3 | woman | 2.2 | 8.8 | Remote symptomatic | Stroke | No retardation | Loc rel[1] symptomatic | Cardiac arrest following cardiomyopathy |
| 4 | man | 1.8 | 11.7 | Remote symptomatic | Cerebral palsy | IQ < 70 | Loc rel[1] symptomatic | Pulmonary infection |
| 5 | man | 2.0 | 10.4 | Remote symptomatic | Cerebral palsy, microcephaly | IQ < 70 | SGE[2] other | Probable suffocation during epileptic seizure |
| 6 | man | 3.3 | 6.7 | Remote symptomatic | Neuronal ceroid lipofuscinosis | IQ < 70 | Lennox-Gastaut | Aspiration pneumonia causing shortness of breath |
| 7 | woman | 0.4 | 6.1 | Remote symptomatic | Holoprosencephaly | IQ < 70 | LR[1] symptomatic | Hydrocephalus with a shunt obstruction |
| 8 | woman | 11.3 | 13.5 | Remote symptomatic | Microcephaly, hydrocephalus internus | IQ < 70 | Isolated SE < enrollment | Intra-cerebral haemorrhage |
| 9 | man | 8.1 | 13.5 | Remote symptomatic | Translocation chromosome 4/15 | IQ < 70 | SGE[2] other | Unknown cause: no information available. |

Age, age at enrollment;
SE, status epilepticus;
Loc rel[1], localization related;
SGE[2], symptomatic generalized epilepsy.

**Figure S1: Cumulative proportion reaching a 2-year terminal remission ($TR_E$) during follow-up.**



# APPENDIX 4

## Additional Supporting Information belonging to Chapter 5.

**Subjective health perception**

| | number of subjects | | | | observed number with very good health perception | | | | rate Dutch population | expected number with very good health perception | | | | very good health perception: standardized incidence rate (SIR) with 95% CI | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | non-idio | TR<5yrs | TR>5yrs | idio | non-idio | TR<5yrs | TR>5yrs | | idio | non-idio | TR<5yrs | TR>5yrs | idio | non-idio | | | TR<5yrs | TR>5yrs |
| 12-18 yrs | 50 | 27 | 14 | 63 | 16 | 7 | 3 | 20 | 29,10% | 14,55 | 7,86 | 4,07 | 18,33 | 1,10 (0,63-1,79) | 0,89 (0,36-1,83) | | | 0,74 (0,15-2,15) | 1,09 (0,67-1,69) |
| 18-25 yrs | 89 | 52 | 30 | 111 | 30 | 8 | 7 | 31 | 29,20% | 25,99 | 15,18 | 8,76 | 32,41 | 1,15 (0,78-1,65) | 0,53 (0,23-1,04)# | | | 0,80 (0,32-1,65) | 0,96 (0,65-1,36) |
| 25-35 yrs | 45 | 20 | 16 | 49 | 13 | 4 | 4 | 13 | 29,70% | 13,37 | 5,94 | 4,75 | 14,55 | 0,97 (0,52-1,66) | 0,67 (0,18-1,72) | | | 0,84 (0,23-2,16) | 0,89 (0,48-1,53) |
| total | 184 | 99 | 60 | 223 | 59 | 19 | 14 | 64 | | 53,90 | 28,98 | 17,59 | 65,30 | 1,09 (0,83-1,41) | 0,66 (0,4-1,02)# | | | 0,80 (0,44-1,34) | 0,98 (0,76-1,25) |
| | number of subjects | | | | observed number with good health perception | | | | rate Dutch population | expected number with good health perception | | | | good health perception: standardized incidence rate (SIR) with 95% CI | | | | | |
| | idio | non-idio | TR<5yrs | TR>5yrs | idio | non-idio | TR<5yrs | TR>5yrs | | idio | non-idio | TR<5yrs | TR>5yrs | idio | non-idio | | | TR<5yrs | TR>5yrs |
| 12-18 yrs | 50 | 27 | 14 | 63 | 30 | 17 | 9 | 38 | 62,80% | 31,40 | 16,96 | 8,79 | 39,56 | 0,96 (0,65-1,36) | 1,00 (0,58-1,60) | | | 1,02 (0,47-1,94) | 0,96 (0,68-1,32) |
| 18-25 yrs | 89 | 52 | 30 | 111 | 52 | 37 | 17 | 72 | 59,80% | 53,22 | 31,10 | 17,94 | 66,38 | 0,98 (0,73-1,28) | 1,19 (0,84-1,64) | | | 0,95 (0,55-1,52) | 1,08 (0,85-1,37) |
| 25-35 yrs | 45 | 20 | 16 | 49 | 23 | 14 | 7 | 30 | 57,90% | 26,06 | 11,58 | 9,26 | 28,37 | 0,88 (0,56-1,32) | 1,21 (0,66-2,03) | | | 0,76 (0,30-1,56) | 1,06 (0,71-1,51) |
| total | 184 | 99 | 60 | 223 | 105 | 68 | 33 | 140 | | 110,68 | 59,63 | 36,00 | 134,31 | 0,95 (0,78-1,15) | 1,14 (0,89-1,45) | | | 0,92 (0,63-1,29) | 1,04 (0,88-1,23) |
| | number of subjects | | | | observed number with less than good health perception | | | | rate Dutch population | expected number with less than good health perception | | | | less than good health perception: standardized incidence rate (SIR) with 95% CI | | | | | |
| | idio | non-idio | TR<5yrs | TR>5yrs | idio | non-idio | TR<5yrs | TR>5yrs | | idio | non-idio | TR<5yrs | TR>5yrs | idio | non-idio | | | TR<5yrs | TR>5yrs |
| 12-18 yrs | 50 | 27 | 14 | 63 | 4 | 3 | 2 | 5 | 8,10% | 4,05 | 2,19 | 1,13 | 5,10 | 0,99 (0,27-2,53) | 1,37 (0,28-4,00) | | | 1,76 (0,21-6,39) | 0,98 (0,32-2,29) |
| 18-25 yrs | 89 | 52 | 30 | 111 | 7 | 7 | 6 | 8 | 11,00% | 9,79 | 5,72 | 3,30 | 12,21 | 0,72 (0,29-1,47) | 1,22 (0,49-2,52) | | | 1,82 (0,67-3,96) | 0,66 (0,28-1,29) |
| 25-35 yrs | 45 | 20 | 16 | 49 | 9 | 2 | 5 | 6 | 12,40% | 5,58 | 2,48 | 1,98 | 6,08 | 1,61 (0,74-3,06) | 0,81 (0,10-2,91) | | | 2,52 (0,82-5,89) | 0,99 (0,36-2,15) |
| total | 184 | 99 | 60 | 223 | 20 | 12 | 13 | 19 | | 19,42 | 10,39 | 6,42 | 23,39 | 1,03 (0,63-1,59) | 1,16 (0,60-2,02) | | | 2,03 (1,08-3,46)* | 0,81 (0,49-1,27) |

**Living arrangements**

| | number of subjects | | | | | observed number living with parents | | | | | rate Dutch population | expected number living with parents | | | | | living with parents standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-20 yrs | 71 | 67 | 27 | 52 | 113 | 60 | 49 | 24 | 38 | 95 | 90,03% | 63,92 | 60,32 | 24,31 | 46,82 | 101,73 | 0,94 | (0,72-1,21) | 0,81 | (0,60-1,07) | 0,99 | (0,63-1,47) | 0,81 | (0,57-1,11) | 0,93 | (0,76-1,14) |
| 20-25 yrs | 60 | 44 | 26 | 35 | 95 | 28 | 24 | 11 | 15 | 48 | 48,53% | 29,12 | 21,35 | 12,62 | 16,99 | 46,10 | 0,96 | (0,64-1,39) | 1,12 | (0,72-1,67) | 0,87 | (0,44-1,56) | 0,88 | (0,49-1,46) | 1,04 | (0,77-1,38) |
| 25-30 yrs | 43 | 19 | 13 | 22 | 53 | 3 | 7 | 3 | 4 | 9 | 15,36% | 6,60 | 2,92 | 2,00 | 3,38 | 8,14 | 0,45 | (0,09-1,33) | 2,40 | (0,96-4,94)# | 1,50 | (0,31-4,38) | 1,18 | (0,32-3,03) | 1,11 | (0,51-2,10) |
| 30-35 yrs | 4 | 2 | 1 | 1 | 6 | 0 | 1 | 0 | 0 | 1 | 4,86% | 0,19 | 0,10 | 0,05 | 0,05 | 0,29 | 0,00 | | 10,29 | (0,25-55,70) | 0,00 | | 0,00 | | 3,43 | (0,09-19,2) |
| total | 178 | 132 | 67 | 110 | 267 | 91 | 81 | 38 | 57 | 153 | | 99,84 | 84,69 | 38,97 | 67,23 | 156,27 | 0,91 | (0,73-1,12) | 0,96 | (0,76-1,19) | 0,98 | (0,69-1,34) | 0,85 | (0,64-4,10) | 0,98 | (0,83-1,15) |

| | number of subjects | | | | | observed number living single | | | | | rate Dutch population | expected number living single | | | | | single standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-20 yrs | 71 | 67 | 27 | 52 | 113 | 2 | 0 | 1 | 1 | 2 | 5,62% | 3,99 | 3,77 | 1,52 | 2,92 | 6,35 | 0,50 | (0,06-1,81) | 0,00 | | 0,66 | (0,02-3,67) | 0,34 | (0,01-1,91) | 0,31 | (0,04-1,14)# |
| 20-25 yrs | 60 | 44 | 26 | 35 | 95 | 10 | 2 | 7 | 5 | 14 | 24,03% | 14,42 | 10,57 | 6,25 | 8,41 | 22,83 | 0,69 | (0,33-1,28) | 0,19 | (0,02-0,68)** | 1,12 | (0,45-2,31) | 0,59 | (0,19-1,39) | 0,61 | (0,34-1,03)# |
| 25-30 yrs | 43 | 19 | 13 | 22 | 53 | 19 | 5 | 2 | 8 | 18 | 26,74% | 11,50 | 5,08 | 3,48 | 5,88 | 14,17 | 1,65 | (0,99-2,58)# | 0,98 | (0,32-2,30) | 0,58 | (0,07-2,08) | 1,36 | (0,59-2,68) | 1,27 | (0,75-2,01) |
| 30-35 yrs | 4 | 2 | 1 | 1 | 6 | 1 | 0 | 0 | 0 | 1 | 21,92% | 0,88 | 0,44 | 0,22 | 0,22 | 1,32 | 1,14 | (0,03-6,33) | 0,00 | | 0,00 | | 0,00 | | 0,76 | (0,02-4,22) |
| total | 178 | 132 | 67 | 110 | 267 | 32 | 7 | 10 | 14 | 35 | | 30,78 | 19,86 | 11,46 | 17,43 | 44,67 | 1,04 | (0,71-1,47) | 0,35 | (0,14-0,73)** | 0,87 | (0,42-1,60) | 0,80 | (0,44-1,35) | 0,78 | (0,55-1,09) |

| | number of subjects | | | | | observed number living as couple | | | | | rate Dutch population | expected number living as couple | | | | | couple standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-20 yrs | 71 | 67 | 27 | 52 | 113 | 6 | 1 | 1 | 2 | 6 | 1,76% | 1,25 | 1,18 | 0,48 | 0,92 | 1,99 | 4,80 | (1,76-10,40)** | 0,85 | (0,02-4,72) | 2,10 | (0,05-11,60) | 2,19 | (0,26-7,85) | 3,02 | (1,11-6,56)* |
| 20-25 yrs | 60 | 44 | 26 | 35 | 95 | 15 | 6 | 7 | 8 | 20 | 22,44% | 13,46 | 9,87 | 5,83 | 7,85 | 21,32 | 1,11 | (0,62-1,84) | 0,61 | (0,22-1,32) | 1,20 | (0,48-2,47) | 1,02 | (0,44-2,01) | 0,94 | (0,57-1,45) |
| 25-30 yrs | 43 | 19 | 13 | 22 | 53 | 20 | 2 | 8 | 8 | 22 | 54,43% | 23,40 | 10,34 | 7,08 | 11,97 | 28,85 | 0,85 | (0,52-1,32) | 0,19 | (0,02-0,70)** | 1,13 | (0,49-2,23) | 0,67 | (0,29-1,32) | 0,76 | (0,48-1,15) |
| 30-35 yrs | 4 | 2 | 1 | 1 | 6 | 3 | 0 | 1 | 0 | 4 | 71,11% | 2,84 | 1,42 | 0,71 | 0,71 | 4,27 | 1,05 | (0,22-3,09) | 0,00 | | 1,41 | (0,04-7,85) | 0,00 | | 0,94 | (0,26-2,40) |
| total | 178 | 132 | 67 | 110 | 267 | 44 | 9 | 17 | 18 | 52 | | 40,96 | 22,82 | 14,10 | 21,45 | 56,42 | 1,07 | (0,78-1,44) | 0,39 | (0,18-0,75)** | 1,21 | (0,70-1,93) | 0,84 | (0,50-1,33) | 0,92 | (0,69-1,21) |

| | number of subjects | | | | | observed number in other household | | | | | rate Dutch population | expected number in other household | | | | | other household: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-20 yrs | 71 | 67 | 27 | 52 | 113 | 3 | 17 | 1 | 11 | 10 | 2,58% | 1,83 | 1,73 | 0,70 | 1,34 | 2,92 | 1,64 | (0,34-4,79) | 9,83 | (5,72-15,70)** | 1,44 | (0,04-7,96) | 8,20 | (4,10-14,70)** | 3,43 | (1,64-6,30)** |
| 20-25 yrs | 60 | 44 | 26 | 35 | 95 | 7 | 12 | 1 | 7 | 13 | 5,00% | 3,00 | 2,20 | 1,30 | 1,75 | 4,75 | 2,33 | (0,94-4,81)# | 5,45 | (2,82-9,53)** | 0,77 | (0,02-4,29) | 4,00 | (1,61-8,24)** | 2,74 | (1,46-4,68)** |
| 25-30 yrs | 43 | 19 | 13 | 22 | 53 | 1 | 5 | 0 | 2 | 4 | 3,46% | 1,49 | 0,66 | 0,45 | 0,76 | 1,83 | 0,67 | (0,02-3,74) | 7,61 | (2,46-17,70)** | 0,00 | | 2,63 | (0,32-9,31) | 2,18 | (0,60-5,60) |
| 30-35 yrs | 4 | 2 | 1 | 1 | 6 | 0 | 1 | 0 | 1 | 0 | 2,11% | 0,08 | 0,04 | 0,02 | 0,02 | 0,13 | 0,00 | | 23,70 | (0,63-139,00) | 0,00 | | 47,39 | (1,27-279,0)* | 0,00 | |
| total | 178 | 132 | 67 | 110 | 267 | 11 | 35 | 2 | 21 | 27 | | 6,40 | 4,63 | 2,47 | 3,87 | 9,63 | 1,72 | (0,86-3,08) | 7,56 | (5,27-10,5)** | 0,81 | (0,10-2,92) | 5,42 | (3,36-8,29)** | 2,80 | (1,85-4,08)** |

**Present education of students in cohort**

| | number of subjects | | | | | observed number with special education | | | | | rate Dutch population | expected number with special education | | | | | special education: standardized incidence rate (SIR) with 95% CI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 80 | 40 | 31 | 34 | 117 | 1 | 17 | 0 | 13 | 5 | 1,30% | 1,04 | 0,52 | 0,40 | 0,44 | 1,52 | 0,96 (0,02-5,36) | 32,69 (19,0-52,3)** | 0,00 | 29,41 (15,7-50,5)** | 3,29 (1,07-7,68)* |
| | number of subjects | | | | | observed number with Lower vocational / lower general secondary / pre-university education | | | | | rate Dutch population | expected number with lower vocational / lower general secondary / pre-university education | | | | | lower vocational / lower general secondary / pre-university education: standardized incidence rate (SIR) with 95% CI | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 80 | 40 | 31 | 34 | 117 | 30 | 5 | 11 | 11 | 35 | 33,50% | 26,80 | 13,40 | 10,39 | 11,39 | 39,20 | 1,12 (0,76-1,60) | 0,37 (0,12-0,87)* | 1,06 (0,53-1,89) | 0,97 (0,48-1,73) | 0,89 (0,62-1,24) |
| | number of subjects | | | | | observed number with intermediate vocational education | | | | | rate Dutch population | expected number with intermediate vocational education | | | | | intermediate vocational education: standardized incidence rate (SIR) with 95% CI | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 80 | 40 | 31 | 34 | 117 | 32 | 12 | 11 | 4 | 51 | 32,90% | 26,32 | 13,16 | 10,20 | 11,19 | 38,49 | 1,22 (0,83-1,72) | 0,91 (0,47-1,59) | 1,08 (0,54-1,93) | 0,36 (0,10-0,92)* | 1,32 (0,99-1,74)# |
| | number of subjects | | | | | observed number with higher vocational or university education | | | | | rate Dutch population | expected number with higher vocational or university education | | | | | higher vocational or university education: standardized incidence rate (SIR) with 95% CI | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 80 | 40 | 31 | 34 | 117 | 17 | 6 | 9 | 6 | 26 | 32,30% | 25,84 | 12,92 | 10,01 | 10,98 | 37,79 | 0,66 (0,38-1,05)# | 0,46 (0,17-1,01)# | 0,90 (0,41-1,71) | 0,55 (0,20-1,19) | 0,69 (0,45-1,01)# |

**Highest atained education of employees in cohort**

| | number of subjects | | | | | observed number with lower education | | | | | rate Dutch population | expected number with lower education | | | | | lower education: standardized incidence rate (SIR) with 95% CI | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 56 | 15 | 21 | 25 | 67 | 24 | 8 | 4 | 10 | 26 | 39,00% | 21,84 | 5,85 | 8,19 | 9,75 | 26,13 | 1,10 (0,70-1,64) | 1,37 (0,59-2,69) | 0,49 (0,13-1,25) | 1,03 (0,49-1,89) | 1,00 (0,65-1,46) |
| 25-35 yrs | 38 | 9 | 13 | 10 | 50 | 13 | 4 | 1 | 1 | 17 | 16,50% | 6,27 | 1,49 | 2,15 | 1,65 | 8,25 | 2,07 (1,10-3,55)* | 2,69 (0,73-6,87) | 0,47 (0,01-2,59) | 0,61 (0,02-3,38) | 2,06 (1,20-3,30)** |
| total | 94 | 24 | 34 | 35 | 117 | 37 | 12 | 5 | 11 | 43 | | 28,11 | 7,34 | 10,34 | 11,40 | 34,38 | 1,32 (0,93-1,81) | 1,64 (0,85-2,86) | 0,48 (0,16-1,13) | 0,96 (0,48-1,73) | 1,25 (0,91-1,68) |
| | number of subjects | | | | | observed number with intermediate education | | | | | rate Dutch population | expected number with intermediate education | | | | | intermediate education: standardized incidence rate (SIR) with 95% CI | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 56 | 15 | 21 | 25 | 67 | 27 | 5 | 13 | 9 | 36 | 47,50% | 26,60 | 7,13 | 9,98 | 11,88 | 31,83 | 1,02 (0,67-1,48) | 0,70 (0,23-1,64) | 1,30 (0,69-2,23) | 0,76 (0,35-1,44) | 1,13 (0,79-1,57) |
| 25-35 yrs | 38 | 9 | 13 | 10 | 50 | 21 | 2 | 9 | 8 | 24 | 46,30% | 17,59 | 4,17 | 6,02 | 4,63 | 23,15 | 1,19 (0,74-1,82) | 0,48 (0,06-1,73) | 1,50 (0,68-2,84) | 1,73 (0,75-3,40) | 1,04 (0,66-1,54) |
| total | 94 | 24 | 34 | 35 | 117 | 48 | 7 | 22 | 17 | 60 | | 44,19 | 11,29 | 15,99 | 16,51 | 54,98 | 1,09 (0,93-1,81) | 0,62 (0,85-2,86) | 1,38 (0,16-1,13) | 1,03 (0,60-1,65) | 1,09 (0,83-1,40) |
| | number of subjects | | | | | observed number with higher education | | | | | rate Dutch population | expected number with higher education | | | | | higher education: standardized incidence rate (SIR) with 95% CI | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs |
| 15-25 yrs | 56 | 15 | 21 | 25 | 67 | 5 | 1 | 4 | 5 | 5 | 12,00% | 6,72 | 1,80 | 2,52 | 3,00 | 8,04 | 0,74 (0,24-1,74) | 0,56 (0,01-3,10) | 1,59 (0,43-4,06) | 1,67 (0,54-3,89) | 0,62 (0,20-1,45) |
| 25-35 yrs | 38 | 9 | 13 | 10 | 50 | 4 | 0 | 3 | 1 | 6 | 35,90% | 13,64 | 3,23 | 4,67 | 3,59 | 17,95 | 0,29 (0,08-0,75)** | 0,00 | 0,64 (0,13-1,88) | 0,28 (0,01-1,55) | 0,33 (0,12-0,73)** |
| total | 94 | 24 | 34 | 35 | 117 | 9 | 1 | 7 | 6 | 11 | | 20,36 | 5,03 | 7,19 | 6,59 | 25,99 | 0,44 (0,20-0,84)** | 0,20 (0,01-1,11)# | 0,97 (0,39-2,01) | 0,91 (0,33-1,98) | 0,42 (0,21-0,76)** |

**Employment status**

| | number of subjects | | | | | observed number of students | | | | | rate Dutch population | expected number of students | | | | | students: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 136 | 85 | 54 | 71 | 204 | 78 | 40 | 31 | 34 | 115 | 46,15% | 62,76 | 39,23 | 24,92 | 32,77 | 94,15 | 1,24 | (0,98-1,55)# | 1,02 | (0,73-1,39) | 1,24 | (0,85-1,77) | 1,04 | (0,72-1,45) | 1,22 | (1,01-1,47)* |
| 25-35 yrs | 47 | 16 | 14 | 20 | 57 | 3 | 0 | 1 | 1 | 3 | 2,39% | 1,12 | 0,38 | 0,33 | 0,48 | 1,36 | 2,67 | (0,55-7,83) | 0,00 | | 2,99 | (0,08-16,90) | 2,09 | (0,05-11,60) | 2,20 | (0,46-6,45) |
| total | 183 | 101 | 68 | 91 | 261 | 81 | 40 | 32 | 35 | 118 | | 63,89 | 39,61 | 25,26 | 33,24 | 95,51 | 1,27 | (1,01-1,58)* | 1,01 | (0,72-1,38) | 1,27 | (0,87-1,79) | 1,05 | (0,73-1,46) | 1,24 | (1,02-1,48)* |
| | number of subjects | | | | | observed number being employed | | | | | rate Dutch population | expected number being employed | | | | | being employed: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 136 | 85 | 54 | 71 | 204 | 49 | 12 | 20 | 22 | 59 | 38,56% | 52,44 | 32,78 | 20,82 | 27,38 | 78,66 | 0,93 | (0,69-1,24) | 0,37 | (0,19-0,64)** | 0,96 | (0,59-1,48) | 0,80 | (0,50-1,22) | 0,75 | (0,57-0,97)* |
| 25-35 yrs | 47 | 16 | 14 | 20 | 57 | 37 | 9 | 13 | 9 | 50 | 80,50% | 37,84 | 12,88 | 11,27 | 16,10 | 45,89 | 0,98 | (0,69-1,35) | 0,70 | (0,32-1,33) | 1,15 | (0,61-1,97) | 0,56 | (0,26-1,06)# | 1,09 | (0,81-1,44) |
| total | 183 | 101 | 68 | 91 | 261 | 86 | 21 | 33 | 31 | 109 | | 90,28 | 45,66 | 32,09 | 43,48 | 124,55 | 0,95 | (0,76-1,18) | 0,46 | (0,29-0,70)** | 1,03 | (0,71-1,44) | 0,71 | (0,48-1,01)# | 0,88 | (0,72-1,06) |
| | number of subjects | | | | | observed number being unemployed | | | | | rate Dutch population | expected number being unemployed | | | | | being unemployed: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 136 | 85 | 54 | 71 | 204 | 7 | 2 | 1 | 2 | 8 | 10,75% | 14,62 | 9,14 | 5,81 | 7,63 | 21,93 | 0,48 | (0,19-0,99)* | 0,22 | (0,03-0,79)* | 0,17 | (0,01-0,96)* | 0,26 | (0,03-0,95)* | 0,36 | (0,16-0,72)** |
| 25-35 yrs | 47 | 16 | 14 | 20 | 57 | 1 | 0 | 0 | 1 | 0 | 8,75% | 4,11 | 1,40 | 1,23 | 1,75 | 4,99 | 0,24 | (0,01-1,36) | 0,00 | | 0,00 | | 0,57 | (0,01-3,18) | 0,00 | |
| total | 183 | 101 | 68 | 91 | 261 | 8 | 2 | 1 | 3 | 8 | | 18,73 | 10,54 | 7,03 | 9,38 | 26,92 | 0,43 | (0,18-0,84)** | 0,19 | (0,02-0,69)** | 0,14 | (0,01-0,79)* | 0,32 | (0,07-0,94)* | 0,30 | (0,13-0,59)** |
| | number of subjects | | | | | observed number being disabled | | | | | rate Dutch population | expected number being disabled | | | | | being disabled: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 136 | 85 | 54 | 71 | 204 | 1 | 30 | 2 | 13 | 20 | 1,19% | 1,62 | 1,01 | 0,64 | 0,84 | 2,43 | 0,62 | (0,02-3,44) | 29,66 | (20,0-42,40)** | 3,11 | (0,38-11,3) | 15,39 | (8,24-26,5)** | 8,24 | (5,03-12,7)** |
| 25-35 yrs | 47 | 16 | 14 | 20 | 57 | 3 | 6 | 0 | 5 | 4 | 2,39% | 1,12 | 0,38 | 0,33 | 0,48 | 1,36 | 2,67 | (0,55-7,83) | 15,69 | (5,79-34,4)** | 0,00 | | 10,46 | (3,38-24,3)** | 2,94 | (0,80-7,53)* |
| total | 183 | 101 | 68 | 91 | 261 | 4 | 36 | 2 | 18 | 24 | | 2,74 | 1,39 | 0,98 | 1,32 | 3,79 | 1,46 | (0,4-3,74) | 25,83 | (18,1-35,9)** | 2,05 | (0,25-7,37) | 13,61 | (8,08-21,60)** | 6,33 | (4,06-9,42)** |

**Level of occupation**

| | number of subjects | | | | | observed number with elementary occupational level | | | | | rate Dutch population | expected number with elementary occupational level | | | | | elementary occupational level: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 49 | 12 | 20 | 22 | 59 | 4 | 2 | 0 | 2 | 4 | 15,00% | 7,35 | 1,80 | 3,00 | 3,30 | 8,85 | 0,54 | (0,15-1,39) | 1,11 | (0,14-4,01) | 0,00 | | 0,61 | (0,07-2,19) | 0,45 | (0,12-1,16) |
| 25-35 yrs | 37 | 9 | 13 | 9 | 50 | 1 | 5 | 0 | 0 | 6 | 5,90% | 2,18 | 0,53 | 0,77 | 0,53 | 2,95 | 0,46 | (0,01-2,56) | 9,42 | (3,06-22,0)** | 0,00 | | 0,00 | | 2,03 | (0,75-4,43) |
| total | 86 | 21 | 33 | 31 | 109 | 5 | 7 | 0 | 2 | 10 | | 9,53 | 2,33 | 3,77 | 3,83 | 11,80 | 0,52 | (0,17-1,22) | 3,00 | (1,21-6,19)* | 0,00 | | 0,52 | (0,06-1,89) | 0,85 | (0,41-1,56) |
| | number of subjects | | | | | observed number with lower occupational level | | | | | rate Dutch population | expected number with lower occupational level | | | | | lower occupational level: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 49 | 12 | 20 | 22 | 59 | 26 | 5 | 4 | 9 | 26 | 42,20% | 20,68 | 5,06 | 8,44 | 9,28 | 24,90 | 1,26 | (0,82-1,84) | 0,99 | (0,32-2,31) | 0,47 | (0,13-1,21 | 0,97 | (0,44-1,84) | 1,04 | (0,68-1,53) |
| 25-35 yrs | 37 | 9 | 13 | 9 | 50 | 10 | 1 | 3 | 1 | 13 | 21,60% | 7,99 | 1,94 | 2,81 | 1,94 | 10,80 | 1,25 | (0,60-2,30) | 0,51 | (0,01-2,87) | 1,07 | (0,22-3,12) | 0,51 | (0,01-2,87) | 1,20 | (0,64-2,06) |
| total | 86 | 21 | 33 | 31 | 109 | 36 | 6 | 7 | 10 | 39 | | 28,67 | 7,01 | 11,25 | 11,23 | 35,70 | 1,26 | (0,88-1,74) | 0,86 | (0,31-1,86) | 0,62 | (0,25-1,28) | 0,89 | (0,06-1,89) | 1,09 | (0,41-1,56) |
| | number of subjects | | | | | observed number with intermediate occupational level | | | | | rate Dutch population | expected number with intermediate occupational level | | | | | intermediate occupational level: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 49 | 12 | 20 | 22 | 59 | 15 | 5 | 11 | 7 | 24 | 32,30% | 15,83 | 3,88 | 6,46 | 7,11 | 19,06 | 0,95 | (0,53-1,56) | 1,29 | (0,42-3,01) | 1,70 | (0,85-3,05 | 0,99 | (0,40-2,03) | 1,26 | (0,81-1,87) |
| 25-35 yrs | 37 | 9 | 13 | 9 | 50 | 21 | 2 | 7 | 8 | 22 | 41,20% | 15,24 | 3,71 | 5,36 | 3,71 | 20,60 | 1,38 | (0,85-2,11) | 0,54 | (0,07-1,95) | 1,31 | (0,53-2,69) | 2,16 | (0,93-4,25)# | 1,07 | (0,67-1,62) |
| total | 86 | 21 | 33 | 31 | 109 | 36 | 7 | 18 | 15 | 46 | | 31,07 | 7,58 | 11,82 | 10,81 | 39,66 | 1,16 | (0,81-1,60) | 0,92 | (0,37-1,90) | 1,52 | (0,90-2,41) | 1,39 | (0,78-2,29) | 1,16 | (0,85-1,55) |
| | number of subjects | | | | | observed number with higher vocational or scientific occupational level | | | | | rate Dutch population | expected number with higher vocational or scientific occupational level | | | | | higher vocational or scientific occupational level: standardized incidence rate (SIR) with 95% CI | | | | | | | | | |
| | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | symp | crypto | TR<5yrs | TR>5yrs | | idio | symp | crypto | TR<5yrs | TR>5yrs | idio | | symp | | crypto | | TR<5yrs | | TR>5yrs | |
| 15-25 yrs | 49 | 12 | 20 | 22 | 59 | 4 | 0 | 4 | 3 | 5 | 9,50% | 4,66 | 1,14 | 1,90 | 2,09 | 5,61 | 0,86 | (0,23-2,20) | 0,00 | | 2,11 | (0,57-5,39) | 1,44 | (0,30-4,19) | 0,89 | (0,29-2,08) |
| 25-35 yrs | 37 | 9 | 13 | 9 | 50 | 5 | 0 | 3 | 0 | 8 | 30,60% | 11,32 | 2,75 | 3,98 | 2,75 | 15,30 | 0,44 | (0,14-1,03)# | 0,00 | | 0,75 | (0,16-2,20) | 0,00 | | 0,52 | (0,23-1,03)# |
| total | 86 | 21 | 33 | 31 | 109 | 9 | 0 | 7 | 3 | 13 | | 15,98 | 3,89 | 5,88 | 4,84 | 20,91 | 0,56 | (0,26-1,07)# | 0,00 | | 1,19 | (0,48-2,45) | 0,62 | (0,13-1,81) | 0,62 | (0,33-1,06)# |

## APPENDIX 5

**Additional Supporting Information belonging to Chapter 6**

**Supplementary Table S1.** Course of epilepsy and effect of treatment for 15 subjects with temporary intractability

| Subject | Seizure and epilepsy type | AED[a] | Course of epilepsy | $TR_E$ | Effect AED |
|---|---|---|---|---|---|
| 3 | infantile spasms (West syndrome, tuberous sclerosis) later CPS (Localization related symptomatic epilepsy). Turned out to be mentally retarded during follow-up. | 4 | 1.5 years of seizures without effect AED. After add-on of VGB remission of 22 months, followed by 5 months of monthly CPS. Three months after increase VGB: new remission of at least one year. | <1 | **Effect VGB**, but still seizures in last year. (1 AED at end) |
| 4 | CPS, SPS (Localization related cryptogenic epilepsy) | 6 | 18 months after AED: 6-month remission, followed by 9 months of weekly SPS. Then 1.5-year remission. Stop CLB, CBZ continued. Sometimes SPS caused by emotion. Also nocturnal doubtful seizures. Recurrence after stop AED. | <1 | AEDs slight effect? (1 AED at end) |
| 1 | SPS, CPS, PSG (Localization related symptomatic epilepsy, spastic tetraparesis, tuberous sclerosis) | 5 | No effect of AED in first 5-year follow-up. Intensity of seizures reduced during the last years of extended follow-up, but still monthly CPS. Not intractable: $TR_E$ = 4 months. | <1 | AEDs no apparent effect. (2 AEDs at end) |
| 11[b] | absences, and some TC after 9 years (Idiopathic generalized epilepsy) | 2 | 5 weeks of daily absences: AED. No effect of AED during 5 years of follow-up, despite several increases of dosage. | <1 | Not considered intractable[b]. AEDs no effect. (1 AED at end) |
| 13 | CPS, TC (Localization related symptomatic epilepsy, mentally retarded, mild spastic tetraparesis) | 3 | After 2 PSG: AED. Monthly seizures during 4.5 years despite CBZ & VIG. CBZ replaced by OCBZ. After add-on of CLB: reduction of seizures. | =1 | AEDs slight effect? (2 AEDs at end) |
| 8 | myoclonic, tonic & TC seizures, CPS spasms, absences (West syndrome, tuberous sclerosis, later localization related symptomatic epilepsy) | 3 | After 5.5 years of daily seizures, remission after change to LTG. About 1 year before the end of follow-up transplantation of kidney followed by 5 severe seizures as a result of operation. | >1 | **Effect of LTG**. (1 AED at end) |

| Subject | Seizure and epilepsy type | AED[a] | Course of epilepsy | $TR_E$ | Effect AED |
|---|---|---|---|---|---|
| 12 | TC, atonic and myoclonic seizures, absences (Juvenile myoclonic epilepsy) | 4 | Atonic seizures due to incorrect AED. Change to VPA: after 3 months a 4-month remission, followed by 1 year of weekly absences & myoclonic jerks. Add-on ESM: 3.5-year remission. Later, unsuccessful to stop or reduce AED. | >1 | **Effect of ESM**. (1 AED at end) |
| 14 | absences, CPS, TC & atonic seizures (Localization related symptomatic epilepsy, mentally retarded, spastic diplegia) | 9 | AEDs during 1st 5 years without effect. After 7 years, sporadic CPS; 4 months later: epilepsy is regulated well, although the same 3 AEDs are used as in the 1st 5 years. | >2 | AEDs no apparent effect. (2 AEDs at end) |
| 7 | TC, myoclonic & atonic seizures, SPS, CPS, SE, absences (Symptomatic generalized epilepsy, probably Rett syndrome) | 7 | 3 years of daily seizures without effect AED, followed by 3 years of sporadic CPS. Then, 1 year of daily absences. After that, sporadic absences & periods with daily seizures. Fewer seizures after increase PHB. | >5 | AEDs slight effect? (1 AED at end) |
| 5 | absences, TC (Idiopathic generalized epilepsy) | 2 | No effect AED on daily absences. In 5th and 6th year of follow-up sporadic absences. Increase of absences after withdrawal of one of the AEDs. | >8 | AEDs slight effect? (No AED at end) |
| 9 | CPS, TC (Localization related symptomatic epilepsy, arginino-succinic aciduria) | 7 | Intractable for 4.5 years despite AEDs. During 5th year of follow-up start OCBZ. After 5 months: 7-month remission followed by 2 months of seizures. Add-on LTG no effect: stop. Then $TR_E$ using OCBZ. | >9 | Effect of OCBZ? (1 AED at end) |
| 10 | SPS, CPS (Localization related symptomatic epilepsy, low-grade ganglioglioma) | 5 | Intractable for almost 5 years, followed by anterior temporal lobectomy. $TR_E$ after operation. | >9 | AEDs no effect. (No AED at end) |
| 15[c] | SPS, CPS, PSG (Localization related symptomatic epilepsy, mesial temporal gliosis) | 3 | AED followed by 6-month remission: stop AED (randomized) followed by seizures: restart. Increasing amount of seizures: intractable (candidate surgery). Add-on VGB: after 6 months $TR_E$. | >10 | **Effect of VGB.** (1 AED at end: fear of seizures) |
| 2 | absences, TC & after one year daily myoclonic jerks (Cryptogenic generalized epilepsy with myoclonic absences) | 6 | During the 4th and 5th year of follow-up a gradual reduction of seizure frequency followed by $TR_E$ (not caused by AED changes). Probably benign type of epilepsy. | >10 | AEDs no apparent effect. (No AED at end) |

| Subject | Seizure and epilepsy type | AED[a] | Course of epilepsy | $TR_E$ | Effect AED |
|---|---|---|---|---|---|
| 6 | TC, myoclonic and atonic seizures, absences (Symptomatic generalized epilepsy, Angelman syndrome) | 8 | No effect of AED for 2.5 years. After addition of ESM: two months later $TR_E$. | >12 | **Effect of ESM.** (3 AEDs at end) |

[a]: AED: anti-epileptic drugs used during the first five years of follow-up. [b]: Subject was probably intractable in last year of follow-up based on seizure pattern but was not considered intractable in final year because of inadequate AED. [c]: Subject taking part of our randomized prospective study of early discontinuation of AEDs [39]. SPS: simple partial seizures, CPS: complex partial seizures, SE: status epilepticus, PSG: partial seizures with generalization, TC: tonic clonic seizures. $TR_E$: terminal remission at end of follow-up in years. CLB: clobazam, CBZ: carbamazepine, OCBZ: oxcarbazepine, ESM: ethosuximide, VGB: vigabatrin, VPA: valproic acid, PHB: phenobarbitone, LTG: lamotrigine.

**Supplementary Table S2.** Course of 16 subjects with late-onset intractability

| Subject | Seizure and epilepsy type | AED [a] | Course of epilepsy | Final year follow-up |
|---|---|---|---|---|
| pat 1 | SPS, PSG (Localization related cryptogenic epilepsy) | 3 | AED followed by 6-month remission: stop AED (randomized)[b]. After 3.5 years: 2 PSG: restart AED followed by SPS & TC with increasing frequency: **failure of AED.** | One seizure / month. Unknown since when drug-resistant (3 AEDs at end). |
| pat 2 | Absences (Idiopathic juvenile absence epilepsy changing to localization related cryptogenic epilepsy) | 3 | Absences: AED. One year of sporadic absences, followed by a 1.5-year remission. Stop AED: sporadic absences some of long duration. Seizures changing to more complex partial type. Restart AED: several trials no effect: **failure of AED.** | 1-2 long lasting absence-like and other seizures / week. Probably drug-resistant since 5 years (2 AEDs at end) |
| pat 3 | CPS (Localization related cryptogenic epilepsy with tuberous sclerosis complex diagnosed after years). Turned out to be mentally retarded during follow-up. | 2 | After 9 CPS a 1-year remission followed by 2 months of daily CPS: AED. After 3 months parents stop AED. After 3 months: 1.5 months of daily CPS: restart AED → 2-year remission. Then: 2 months of CPS followed by 1-year remission after increase of AED. This was repeated several times. MRI at age 8 years: normal. | Daily clustered CPS. Probably drug-resistant since 5 years (3 AEDs at end) |
| pat 4 | FC, TC, CPS, absences (At enrollment labeled as idiopathic, later symptomatic generalized epilepsy, premature birth: twins) | 4 | ~14 FC in 1st year of age. At age 1: cluster of 6 TC. After intake 2 TC: AED. Clusters of 1-2 TC / month, some with fever, with remissions of 3-11 months. TC & absences in 3rd year of follow-up: **Nearly intractable**. In 5th year: remission, but CPS in last month. | Light retardation, behavioral problems, and autism. Daily clustered seizures. Probably drug-resistant since 3 years (2 AEDs at end) |
| pat 5 | SE, CPS (Localization related cryptogenic epilepsies) | 1 | Partial SE, after 4 months 1 CPS: start AED. During ~2 years CPS every 1-2 months, with 2 remissions of at least 3 months. Then: 1 CPS / year until five years of follow-up. | CPS every 1-2 months. Multi-focal epilepsy. Unknown since when drug-resistant (3 AEDs at end) |
| pat 6 | TC, CPS, atonic/ astatic seizures, sleep attacks (Symptomatic generalized epilepsy with myclonic-astatic seizures, mentally retarded) | 3 | ~10 seizures within 2 weeks followed by 1-year remission. TC & CPS: AED. Also atonic/astatic seizures & sleep attacks. After 10 months a 3-year remission: stop AED. After 1.5 years: 8 months of CPS. Successful restart of AED. | Symptomatic multi-focal epilepsy: 1-2 TC & other seizures daily. Some may be related to behavior. Probably drug-resistant since 5 years. (2 AEDs at end) |

| Subject | Seizure and epilepsy type | AED [a] | Course of epilepsy | Final year follow-up |
|---|---|---|---|---|
| pat 7 | CPS, TC, absences (Lennox Gastaut syndrome, mentally retarded) | 2 | During 2.5 months CPS before intake: AED. After 4.5 months of seizures, remission until 5 years of follow-up. Used AED for 2.5 years. Recurrences 8 years after stop AED: restart AED no effect, however EEG differed from earlier EEGs as well as the seizures. **Failure of AEDs??** | ~ 2 TC / month & absences. Probably drug-resistant since 5 years (4 AEDs at end) |
| pat 8 | infantile spasms, PSG, SPS & CPS (West syndrome, mentally retarded) | 4 | During 1.5 months infantile spasms & PSG: AED. Remission of 1 year: stop AED. After 6 months: 2-month period of PSG, SPS & CPS: restart AED. After 7 months of seizures: 2-year remission followed by 2 PSG. | Frequent absences & atonic seizures. Unknown since when drug-resistant (1 AED at end) |
| pat 9 | SPS, CPS, PSG (Localization related cryptogenic epilepsy, multifocal). Turned out to be mentally retarded during follow-up. | 3 | 2 PSG within 3 weeks: AED. Within 2 months 2 CPS. A 9-month remission. PSG and after 1 month SPS. Then 9-month remission: 2 unclear events within 1 month. Then 8-month remission: in next 8 months 11 SPS, CPS, and PSG. Extra AED: 1 seizure / year. | Despite several trials of AEDs 1 seizure / week. Unknown since when drug-resistant. (2 AEDs at end) |
| pat 10 | Atypical absences, TC (Symptomatic generalized epilepsy, mild physical handicap, mentally retarded) | 2 | 3 years of absences: AED. After 6 months: 1-year remission. During 1 month: daily staring. After 4 months: TC with fever. Then 2.5-year remission followed by absences during 3 months. | Daily seizures. Unknown since when drug-resistant (1 AED at end) |
| pat 11 | CPS, PSG (Localization related symptomatic epilepsy, microcephaly, mentally retarded) | 3 | 1 month of weekly CPS: AED. During 8 months CPS in reducing numbers. A 7-month remission. Then 3 CPS within 6 weeks followed by 1-year remission. 1 unclear event and a 2$^{nd}$ after 2 month. After 1.5-year remission: PSG. | One seizure / month. Four years before: sporadic seizures. Unknown since when drug-resistant (1 AED at end) |
| pat 12 | SE with fever, myoclonic jerks, CPS (Localization related symptomatic epilepsy, multifocal, severe encephalopathy after SE, mentally retarded) | 2 | SE. After 8 years: 10 months of daily myoclonic jerks & CPS: AED→1-year remission: stop AED (randomized)[b]. A 3-month remission followed by 3 months of myoclonic jerks. After 2-year remission: 6 months of myoclonic jerks: not regarded as epilepsy: normal EEG. Restart AED after increase of seizures 9 years after intake (no info of effect). After 3 years abnormal EEG: add-on LTG (no info of effect). | Monthly myoclonic jerks. Probably drug-resistant since 8 years (2 AEDs at end) |

| Subject | Seizure and epilepsy type | AED [a] | Course of epilepsy | Final year follow-up |
|---|---|---|---|---|
| 13 | FC, SE, CPS, PSG (Localization related symptomatic epilepsy, spastic tetraparesis). Turned out to be mentally retarded during follow-up. | 2 | FC at age five. After 4 months SE: AED. After 6-month remission: 6 months of sporadic CPS & PSG. AED change: CPS after 3 months, CPS after 1 month. After a 1-year remission: CPS. A 2-year remission until 5 years after intake. | After at least 7 years of remission relapse. At end monthly increase of CPS and sporadic PSG. Probably drug-resistant since 4 years (2 AEDs at end) |
| 14[c] | Atypical absences (Generalized idiopathic epilepsy changing to symptomatic generalized epilepsy). Turned out to be mentally retarded during follow-up. | 2 | ~3 months of absences: AED. After 5 months of sporadic absences 1-year remission: stop AED. After 5 months: absences during 3 months. Restart of AED: 19 months of remission followed by daily absences until end of 5-year follow-up: 2nd AED no effect. | 20 absences/day. Sometimes falls down or is photosensitive. Drug-resistant since ~8 years (2 AEDs at end) |
| 15[c] | CPS, PSG, SE (Localization related cryptogenic epilepsy) | 1 | 3 PGS & 1 SE within 3.5 months: AED. During period of 3 years: 3-6 seizures/year. Next: 2 years with no remissions of more than 3 months. During further follow-up sporadic periods of remission (≤ 1 year, sometimes without AED). | 2-3 seizures/month. Unknown since when drug-resistant (2 AEDs at end) |
| 16[c] | CPS (Localization related symptomatic epilepsy) Tuberous sclerosis with normal intelligence | 1 | During 5 weeks 1 CPS/day: AED→6-month remission: stop AED (randomized)[b]. After 4 months CPS: restart AED without effect: **failure of AED**. During 4 years only 2 remission periods of 3 months. | 1-2 CPS /month Unknown since when drug-resistant (1 AED at end) |

[a]: anti-epileptic drugs used during the first five years of follow-up. [b]: subjects taking part of our randomized prospective study of early discontinuation of AEDs [39]. [c]: intractable seizure pattern during first five years of follow-up, but had not enough AEDs or too shortly to be considered intractable in these years. SPS: simple partial seizures, CPS: complex partial seizures, TC: tonic clonic seizure, PSG: partial seizure with generalization, SE: status epilepticus, FC: febrile convulsion. LTG: lamotrigine.