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REVIEW

Prognostic factors for medically intractable epilepsy: A systematic review

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Summary
Objective: One third of all epilepsy patients have medically intractable epilepsy. Knowledge of prognostic factors that, in an early therapeutic stage of epilepsy, herald intractability could facilitate patient management. In this systematic review, we examined the evidence for independent prognostic factors of intractability in patients with epilepsy.
Methods: MEDLINE and EMBASE were searched for cohort studies reporting on prognostic factors for medically intractable epilepsy. After selection of abstracts, full-text articles were obtained and their quality was assessed by two reviewers, using the QUIPS checklist. All independent prognostic factors in the individual studies were summarized.
Results: Eleven cohort studies were included, of which ten hospital-based. Younger age at seizure onset, symptomatic etiology, high initial seizure frequency, medical history, epileptic EEG abnormalities, and failure of previous antiepileptic-drugs (AEDs) were documented as independent prognostic factors of intractability in at least 2 of the 11 studies; none of these factors was reported in all 11 studies. None of the studies considered genetic, neurobiological, or immunological factors. The studies were of moderate quality, mostly because they did not provide a conceptual model for the choice of predictors. Heterogeneity in study design, population, candidate prognostic factors, and outcome definitions precluded statistical pooling.

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Conclusions: While potentially relevant prognosticators of medically intractable epilepsy have been identified, the evidence for these factors is not consistent. There is a need for well-designed prognostic population-based cohort studies that also include pharmacological, genetic, neurobiological, and immunological factors. A valid model for the early prediction of medically intractable epilepsy could improve patient management.

Contents

Introduction

Epilepsy, one of the most common neurological disorders (Hauser et al., 1993; Sander, 2003; Shackleton et al., 1997; Siniatchkin and Koepp, 2009), can be classified into symptomatic versus idiopathic or, focal versus generalized forms, based on its etiology (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). This classification is important in determining the appropriate antiepileptic-drug (AED) treatment strategy. Focal epilepsy tends to respond to the majority of AEDs (Luders et al., 2009) but is also more frequently associated with intractability (Devinsky, 1999). Intractability (i.e. refractoriness or pharmacoresistance) is defined as failure of adequate trials of two tolerated, appropriately chosen and used AED schedules to achieve sustained seizure freedom (Kwan et al., 2010). This definition was proposed by a taskforce of the International League against Epilepsy in response to different existing definitions of intractability regarding required number of drug failures, endpoint (e.g., seizure freedom versus tolerable seizure load), and time to achieve this endpoint (Berg, 2009). Overall, it is estimated that a third of all patients have intractable epilepsy (Johnston et al., 2009; Panayiotopoulos, 2007; Sander, 2003) though these patients may experience periods of seizure remission (Munger Clary and Choi, 2011). Intractable patients have a higher risk of premature death, injuries, psychosocial dysfunction, and reduced quality of life (Hao et al., 2011). There are, however, large differences in individual responses to AEDs even between patients with seemingly identical seizure types and epilepsy syndromes (Schmidt and Loscher, 2005).

In clinical practice, intractability is often identified only after several AEDs have been tried. It is difficult to predict at an early stage who will develop intractable epilepsy, except for patients with relatively rare entities such as Lennox–Gastaut syndrome (Berg, 2009). Several clinical, etiological, demographic, pharmacological, and genetic factors may be involved in the development of intractability. Knowledge of those independent factors that predict intractability as early as possible could improve patient management by guiding treatment decisions, such as earlier referral for epilepsy surgery. This may alleviate the medico-social and economic burden of intractable epilepsy (Hao et al., 2011).

The aim of this systematic review was to summarize and qualify the results of published cohort studies designed to find independent prognostic factors of intractability in epilepsy patients.

Methods

Search strategy and selection criteria

A systematic search was conducted using MEDLINE and EMBASE, until June 10, 2010. The search was designed to identify (retrospective or prospective) cohort studies, since this is considered the optimal design for evaluating predictors and outcome (Berg, 2009; Moons et al., 2009). The studies had to be published as full reports in English with the aim of identifying independent prognostic factors of intractability in patients diagnosed with epilepsy. The search

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strategy was developed in collaboration with a medical information specialist and is included in Appendix 1. The reference lists of all relevant publications were checked for additional published studies not found by our electronic search.

All retrospective and prospective cohort studies were included if they met the following criteria: (a) focus on patients diagnosed with epilepsy, (b) had intractability, refractoriness, or pharmacoresistance of epilepsy as an outcome, i.e. defined by failure of adequate AED trials, (c) aimed to identify prognostic factors out of a larger set of candidate predictors, and (d) assessed independent prognostic factors using multivariable analysis, a prerequisite to identify independent predictors of a studied outcome (Moons et al., 2009). Thus only studies designed as prognostic studies, i.e. to establish the probability of the outcome (intractability) were included. Studies that focused on the (etiologic) association of a single prognostic variable were therefore excluded. In the case of repeated studies within the same cohort, the one with the longest follow-up or largest study population was included or, if equal, the most recent report was included. Two reviewers (MW and SU) independently applied these selection criteria to all titles and abstracts, and reviewed and discussed potentially relevant full papers.

We excluded studies that assessed prognostic factors of remission even though intractability has often been defined as failure to enter seizure remission (Sillanpaa and Schmidt, 2011). Remission can be a temporary phenomenon in patients with pharmacoresistant epilepsy and therefore remission does not necessarily exclude intractability (Munger Clary and Choi, 2011). Moreover, the nature of prognostic research implies that risk factors are not necessarily causally related to the outcome (Moons et al., 2009; Tripepi et al., 2008) and this means that factors predictive of remission are not directly in its 'negative form' predictive of intractability.

Data extraction and quality assessment

Two reviewers independently (MW and SU) extracted data and assessed the risk-of-bias of the selected studies, using standardized forms to ensure the reliability of collected data. Data were extracted on:

- cohort: name, aim, and publication characteristics (authors, year of publication, journal);
- study design: retrospective or prospective cohort, hospital- or population-based, follow-up duration, and type of analysis;
- study population and recruitment characteristics: age, gender, type of epilepsy, treatment provided, number of subjects included in cohort and analysis, inclusion and exclusion criteria, country, year and setting of recruitment, type of data and method of data collection;
- prognostic factors: type and number of candidate factors, and type and number of independent prognostic factors from multivariable analysis including association measures (effect size and 95% confidence interval, CI);
- outcome: definition and prevalence.

The methodological quality of the studies was assessed using the Quality In Prognosis Studies (QUIPS) tool, which is designed for systematic reviews of prognostic factor studies (Hayden et al., 2006). QUIPS contains six categories assessing risk of bias issues related to: (1) patient selection, (2) study attrition, (3) measurement of the studied prognostic factors, (4) measurement of the outcome, (5) multivariable adjustment for other prognostic factors, and (6) statistical analysis and reporting. For each study, all six categories were scored separately as being of high, moderate or low quality; i.e. presenting a low, moderate, or high risk of bias, respectively.

Data analysis

All independent prognostic factors identified by multivariable analysis in individual studies are presented, including their estimated effect size (e.g., odds or hazard ratio) and 95% confidence interval (CI). Quantitative pooling of results proved impossible because of heterogeneity in study design, study population, type of prognostic factors, and outcome definitions in the studies. For this reason, a formal and clinically relevant meta-analysis unfortunately could not be performed.

Results

Literature selection

Fig. 1 presents a flow diagram of the study selection process. The search strategy (MEDLINE and EMBASE) and reference checking yielded 3112 citations. A total of 54 articles were potentially relevant and were retrieved in full text. Of these, 43 were excluded: 18 because they considered the prognosis of a related outcome such as seizure remission, 13 because they did not perform a multivariable analysis and 10 since they were no cohort or non-English studies. Another 2 (Berg et al., 2009; Schiller and Najjar, 2008) were excluded because data came from the same cohort. This resulted in 11 studies to be included in our analysis.

Study characteristics and methodological quality

Details of the characteristics of the 11 included studies are listed in Table 1. The outcome 'intractability' varied in terms of the number of AEDs tried, tolerated number of seizures, and the duration of seizure-free periods. Only one cohort study was population-based (Berg et al., 2001) whereas all other cohorts were hospital based. There was considerable variation among studies with respect to population size (89—780), duration of follow-up (from some months up to 17 years), and the proportion of intractable cases (7—79%). Most studies included patients with both focal and generalized epilepsies, however three studies considered only patients with focal epilepsy (Aikia et al., 1999; Dlugos et al., 2001; Ohtsuka et al., 2001). Six cohorts included only children (at least < 20 years of age), two only adults, and three patients of all ages. The results of the quality assessment are presented in Table 2. The quality of most studies was moderate, mainly because study attrition was often

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Table 1 Characteristics of included studies.

Study	Cohort (country, year)	Design	Type of analysis	*N* included	Follow up	Epilepsy type (% focal epilepsy)	Gender (% males)	Age (years) (range/mean)	Outcome	*N* (%) intractable epilepsy
Aikia et al. (1999)	Finland (ng)	Prospective, longitudinal hospital based	Logistic regression	89	2 years	Focal epilepsy (100%)	49%	Range: 15–63	Poor 2-year seizure outcome; refractory seizures despite adequate drug treatment; refractory if >1 generalized or >4 partial seizures occurred during 1 y	10 (11%)
Berg et al. (2001)	US (1993–1997)	Prospective, longitudinal hospital & population based	Cox proportional hazards regression	599	At least 1.5 years Median 5 years	All types (53%)	49%	Range 0–15 Median 5.3	Lack of seizure control by 2 AEDs with >1 seizure/month over 18 months	60 (10%)
Dlugos et al. (2001)	US (1999)	Retrospective, longitudinal outpatient hospital based	Logistic regression	120	>2 years	Temporal lobe epilepsy (100%)	53%	Range 1–18	Persistent seizures involving impairment of consciousness between 18 and 24 months after epilepsy despite at least 2 AED trials	45 (38%)
Hitiris et al. (2007)	Scotland (1982–2001)	Prospective, longitudinal hospital based	Logistic regression	780	2.5–21 years	All (% not given)	52%	31 years (range 9–93 years)	Not achieving seizure freedom for at least the last 12 months of follow up	318 (41%)
Hui et al. (2007)	Hong Kong, China (>1997)	Prospective, longitudinal hospital based	Logistic regression	260	Mean 7 years (1–17 years)	All (90% symptomatic/cryptogenic)	49%	Range 15–79 34	Seizures despite 2 AEDs	103 (40%)
Ko and Holmes (1999)	USA (ng)	Retrospective, cross sectional hospital based	Logistic regression	183	Mean 5.3 year (intractable) Mean 4.9 year (well controlled)	All (% not given)	51%	Mean 2.9 years (intractable) Mean 5.3 years (controlled)	Continued seizures despite adequate trials of 3/more AEDs	144 (79%)
Kwong et al. (2003)	Hong Kong, China (<1997)	Prospective, longitudinal hospital based	Logistic regression	255	>2years	All (50%)	Not given	<15 years	Uncontrolled seizures; at least one seizure/month over 2y period despite treatment with ≥3 different AEDs administered singly or in combination	44 (17%)
Ohtsuka et al. (2001)	Japan (1992–1994)	Retrospective, longitudinal hospital based	Logistic regression	113	>3 years	Symptomatic/cryptogenic (%not given)	Not given	Not given	Average seizure frequency of one/more per month during the 6 months before last follow up	40 (35%)
Oskoui et al. (2005)	Canada (1991–2000)	Retrospective (hospital based)	Logistic regression	196	55 months (24–163 months)	All (57%)	50%	7.6 (SD 3.7)	Seizures recurring at least monthly for more than a year associated with failure of ≥3 AED trials	12 (6.9%)
Ramos-Lizana et al. (2009)	Spain (1994–2004)	Prospective, longitudinal, hospital based	Cox proportional hazards regression	343	Mean 76.2 months (range 24–239 months)	All (63%)	56%	4.8 years (SD 3.8)	Lack of seizure control (.1 seizure per month for ≥18 months and no more than 3 consecutive months seizure freed during this interval) by >2 AED trials at maximum tolerated dose	30 (8.7%)
Schiller (2009)	Israel (1999–2005)	Prospective, longitudinal hospital based	Logistic regression	256	Mean 3.7 years (2–8.5 years)	All (63%)	45%	32 (SD 15.8)	Drug resistance after more than 1 year seizure remission	41 (16%)

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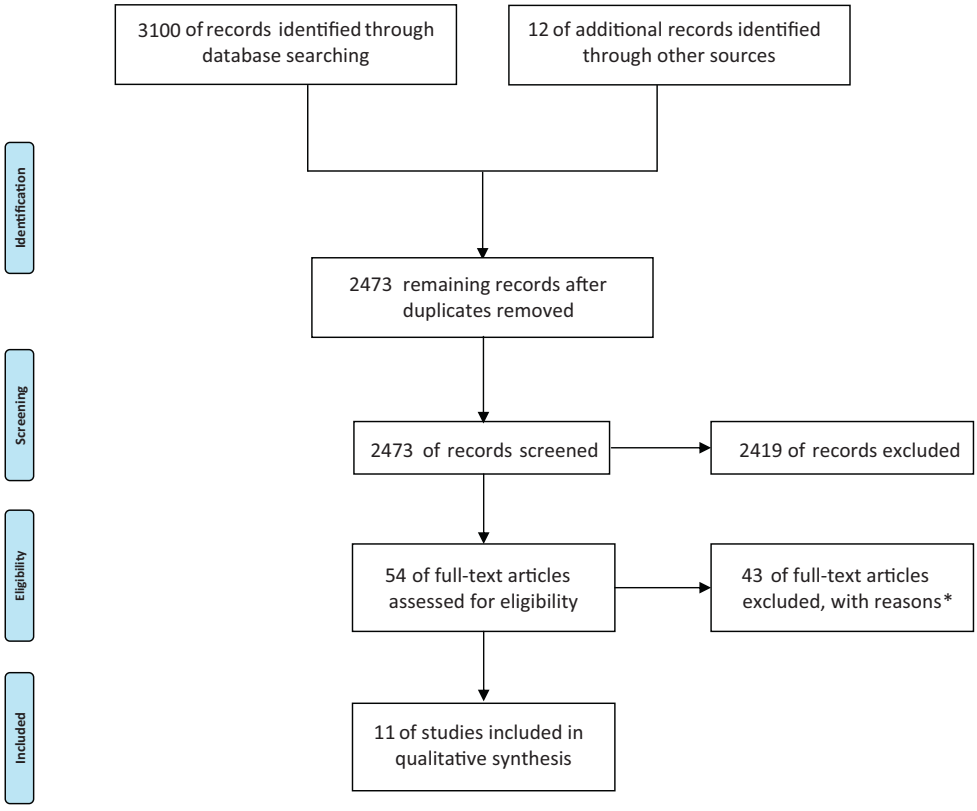

* Non English language (n=4), No cohort study (n=6), Prognosis other outcome (f.e. seizure recurrence or remission) (n=18), No multivariate analysis (n=13), Studies on already included cohort (n=2)

Figure 1 Flow diagram of literature search process (41).

inadequately described and they lacked a conceptual model for the choice of candidate prognostic factors investigated.

Prognostic factors

Table 3 lists the different types of candidate prognostic factors initially considered in each study and indicates which factors were found significant in predicting intractability. Definition and categorization of most factors were different from study to study, e.g. how seizure frequency was measured before and after treatment and at which time intervals (daily/ weekly/ monthly, etc.), or a combination of several medical history items was taken as one early risk factor. Not all studies addressed all type of factors, i.e. not one factor was considered in all eleven studies. For

Table 2 Results of the quality assessment of individual studies; assessed by QUIPS (Hayden et al., 2006).

	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Aikia et al. (1999)	+/−	−	+/−	+/−	+/−	+/−
Berg et al. (2001)	+	−	+/−	+/−	−	+/−
Dlugos et al. (2001)	+	−	+/−	+/−	+/−	+/−
Hitiris et al. (2007)	+	−	+/−	+	+/−	+
Hui et al. (2007)	+/−	−	+/−	+/−	+/−	+
Ko and Holmes (1999)	+/−	−	+/−	+/−	+/−	+/−
Kwong et al. (2003)	+/−	−	+/−	+/−	+/−	+
Ohtsuka et al. (2001)	+/−	−	+/−	+/−	+/−	−
Oskoui et al. (2005)	+/−	+	+/−	+/−	+/−	−
Ramos-Lizana et al. (2009)	+	−	+/−	+/−	+/−	+/−
Schiller (2009)	+/−	−	+/−	−	+/−	+

+ denotes a high quality; +/− denotes a moderate quality; − denotes a low quality.

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Table 3 Type of candidate prognostic factors considered in each study.

	Demography (age at onset)	Demography (gender)	Epilepsy classification (symptomatic or idiopathic)	Seizure type (focal or generalized)	Seizure frequency	Medical history (febrile seizures, status epilepticus, mental retardation, etc.)	Test characteristics (EEG, MRI, neuropsychology)	Pharmacology	Genetic factors or biomarkers
Aikia et al. (1999)	X		X	X	v		X		
Berg et al. (2001)	X	v	X	X	X	X	X		
Dlugos et al. (2001)	v			na[a]		X	X	X	
Hitiris et al. (2007)		v	X		X	X			
Hui et al. (2007)	v	v	X			X		v	
Ko and Holmes (1999)	X		X	X	v	X	X		
Kwong et al. (2003)	v		v	v	X	X	v		
Ohtsuka et al. (2001)	v	v	X	X	X	X	v		
Oskoui et al. (2005)	v	v	v	X	X	X	v		
Ramos-Lizana et al. (2009)	X	v	X	v	X	v	v	X	
Schiller (2009)		v	v	v	v	v	v		

v = factors considered as potential prognostic to be included in (either univariable or multivariable) analysis not found significant in multivariable analysis.
X = factors considered as potential prognostic to be included in (either univariable or multivariable) analysis and found significant by multivariable analysis.
[a] Not applicable since only addressing temporal lobe epilepsy.

example, age at onset was not taken into account in two of the included studies. Pharmacological factors were rarely included, and genetic factors or biomarkers, such as neurobiological or immunological factors, were not considered as potential prognostic factors in any of the studies.

Independent prognostic factors reported at least twice were: younger age at epilepsy onset, focal seizures (either simple or complex), a high seizure load, a history of febrile seizures or status epilepticus, a positive family history, and an abnormal neurodevelopment as well as EEG containing both epileptic (spikes or spike waves) and non-epileptic abnormalities (slowing). Two of the three studies that assessed the failure of previous AED attempts showed AED failure to be important with a large effect size (OR ranged from 9.7 to 93). Furthermore, an idiopathic etiology was associated with a lower risk of developing intractable epilepsy. Gender was not identified as a predictor of intractability in any of the studies. A detailed overview of the prognostic factors identified by multivariable analysis in the individual studies is provided in Appendix 2, including their odds- or hazard ratios and 95% confidence intervals.

Discussion

This systematic review summarizes the evidence for independent prognostic factors for medically intractable epilepsy derived from eleven identified cohort studies. Although the heterogeneity, and inconsistent results meant that the evidence for any individual factor was limited, several prognostic factors were identified. Included studies were mostly of moderate quality, frequently lacked a conceptual model for the choice of candidate prognostic factors and inadequately described study attrition. The moderate quality of included studies may have influenced the reported results, with high quality studies presumably providing the most reliable prognostic factors. However, we refrained from weighing the quality items or using a summary score since this is often difficult to justify (which quality item to assign as most important), and potentially misleading since a low quality score may also reflect poor reporting (Hayden et al., 2006; Juni et al., 1999; Riley et al., 2007; Whiting et al., 2005). The inconsistency in independent predictors of intractability across studies may also result from multicollinearity between several factors. For example, age at onset, EEG or MRI characteristics as such may be associated with intractability yet not consistently found predictive by multivariable analysis. These factors may be correlated to epilepsy classification or medical history and thus may not turn out a valid individual predictor of intractability.

The strongest prognostic factors were symptomatic etiology and focal seizures; however, studies define and classify these factors differently, which makes it difficult to draw firm conclusions. The use of different definitions is a problem in epilepsy research in general, and for this reason Berg et al. recently suggested revised terminology and concepts for epilepsy and seizure classification, to facilitate comparisons among studies (Berg et al., 2010). Younger age at onset, a high initial seizure frequency, epileptic EEG abnormalities, and several clinical items, such as a history of febrile seizures, status epilepticus, and a neurodevelopmental

delay, were also found to predict intractability, reflecting the multifactorial character of intractable epilepsy.

Presented factors are in accordance with results from other studies that also reported symptomatic etiology to be associated with a higher rate of intractability (Devinsky, 1999; Kwan et al., 2011; Mohanraj and Brodie, 2006). Although applying the same determinants and outcome, these studies were not specifically designed as prognostic cohort studies, and did not assess factors out of a larger set of candidate predictors by multivariable analysis.

Several large cohort studies have been performed on the prediction of seizure remission, among which the UK National General Practice Study of Epilepsy (Cockerell et al., 1997) and the Dutch Study of Epilepsy in Childhood (Geerts et al., 2010). These identified prognostic factors such as idiopathic etiology, related to long lasting seizure remission as the opposite of intractability (Cockerell et al., 1997; Geerts et al., 2010). Similar studies not designed as predictor-finding studies, found an older age at onset, a low seizure load and a normal EEG to be associated with long lasting seizure remission (Arts et al., 2004; Camfield et al., 1993; Collaborative Group for the Study of Epilepsy, 1992; MacDonald et al., 2000; Shafer et al., 1988; Sillanpaa and Schmidt, 2009). Though this may strengthen the findings in our review, these studies were not included in this review since seizure remission does not necessarily imply 'tractable epilepsy'. Furthermore, as the nature (causal or non causal) of risk factors is irrelevant in prognostic research, risk factors in their 'negative form' may not be predictive for a reverse outcome (Moons et al., 2009; Tripepi et al., 2008). Factors found to be predictive for intractability are thus not necessarily in their 'negative form' predictive of seizure remission.

Few studies considered pharmacological factors. Two studies assessing failure of previous AED attempts found treatment failure to be prognostic of intractability with a convincingly large effect size (Dlugos et al., 2001; Schiller, 2009). Failure of adequate AED trials is inextricably linked to intractable epilepsy. Usually it is incorporated in the definition of intractability (although this was only explicitly stated in six of the included studies). In these cases failure of AED trials becomes self-evident and can no longer be considered as a prognostic factor. In clinical practice, when the aim is to predict intractability as early as possible, i.e. soon after diagnosis, repeated AED failure as prognostic factor is not going to be very helpful. Again, a clear and uniform definition of 'early' prediction is essential, which was not given in the studies under review.

Many researchers have suggested that genetic or autoimmune mechanisms have a role in epileptogenesis (Lazarowski and Czornyj, 2011; Sillanpaa and Schmidt, 2011; Zarczuk et al., 2010), and several studies have demonstrated specific genotypes or biomarkers to be associated with intractable epilepsy (Kasperaviciute and Sisodiya, 2009; Schmidt and Loscher, 2005; Sisodiya and Marini, 2009). Surprisingly, neither neurobiological, immunological markers, nor genetic factors have been investigated as potential prognostic factors in the multivariable analysis in the retrieved cohort studies. As early as 1992, the Collaborative Group for the Study of Epilepsy stated that research should focus on biological markers to ascertain the origin of AED resistance (Collaborative Group for the Study of Epilepsy, 1992). Sillanpaa and Schmidt, recently concluded that current research misses important factors that determine or predict seizure outcome in (childhood-onset) epilepsy and suggest several neurobiological factors as candidate factors (Sillanpaa and Schmidt, 2011).

Although the eleven studies identified factors associated with intractability, firm statements on independent factors and their prognostic value are not possible. Qualifications of our findings are complicated by heterogeneity in population, design, outcome definitions, and prognostic factor characterization, which precluded meta-analysis of the data. Potential prognostic factors do not come out consistently. This may be due to the choice of prognostic factors or because studies only presented statistically significant factors, whereas lack of significance does not necessarily imply lack of prognostic value, as studies may have been underpowered to detect factors of prognostic value (Bentzen, 2001). We included cohort studies consisting of newly diagnosed as well as chronic epilepsy patients with varying durations of follow-up. This may have influenced the intractability rates that were reported and could have influenced the factors that were found to be prognostic. None of the included studies examined interactions between variables, such as epilepsy classification and age of onset, (presumed) genetic etiology, or EEG characteristics (Berg et al., 2010). Studies also used different definitions of the outcome of therapy (seizure reduction or seizure freedom) and of the duration of seizure-free periods. This again highlights the need for standardized definitions (Kwan et al., 2010). We were not able to pool data to perform a meta-analysis or to stratify data by clinically important subgroups (such as focal versus generalized epilepsies).

Moreover, the evidence provided comes mainly from hospital-based cohorts. The included studies mainly involve patients receiving specialized care, probably because of diagnostic certainty in these patients. However, these are likely to include the more difficult-to treat patients complicating the study of predictors of intractability requiring the inclusion of a representative group. In population-based studies, lack of diagnostic certainty may give rise to biased estimates of intractability which may be a major drawback as certainty about the diagnosis of epilepsy is crucial in studies related to intractability, as is epilepsy classification (Cockerell et al., 1997), in itself an issue that is very much debated. Yet only large well-defined prospective population-based cohort studies are appropriate to identify the effects of multiple potential prognostic factors and their interactions (Berg, 2009), if a strict definition of the outcome, i.e. intractable epilepsy is applied. To limit heterogeneity and for feasibility and generalization purposes, the ideal study population should encompass all new-onset epilepsies from the general population, especially if the aim is to predict intractability as early as possible. In these patients maximal efforts should be made to accurately characterize the seizure and epilepsy type and include all potential prognosticators ranging from demographic items, seizure and medical history, and diagnostic tests (neurological exam, EEG, MRI, as well as immunological or genetic markers). The latter may include autoimmune markers (such as anti-glutamate receptor antibodies) or candidate genes such as SCN1A that are already tested for certain clinical management purposes. These genetic mutations are related to specific etiology, still

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they may provide important additional prognostic information or even make others, for example phenotype that may be more difficult to characterize, redundant. Genome wide screening is not feasible for inclusion in prognostic research, however several identified epigenetic mechanisms as the REST-factor (Roopra et al., 2012; Weaver and Pohlmann-Eden, 2013) may be worthwhile testing for its prognostic value for intractable epilepsy. The choice of potential prognostic factors should thus be chosen depending on current literature taking into account the number of patients to be included and the availability of data in daily practice.

Conclusion

A symptomatic etiology and focal seizures, younger age at onset, a high initial seizure frequency, epileptic EEG abnormalities, and several clinical items such as a history of febrile seizures, status epilepticus, and neurodevelopmental delay, have been identified as potential predictors of intractable epilepsy. However, the lack of study homogeneity, inconsistency in assessed candidate factors, as well as the bias toward hospital-based studies means that the evidence does not yet provide a clinically reliable picture. No single factor could be convincingly identified as independent early predictor of intractability.

We believe that additional, well-designed prospective population-based cohort studies are warranted. These should consider the predictors identified in this review, but also new predictors such as pharmacological, genetic, neurobiological, and immunological factors. Such a systematic study could lead to the development of a prediction model for clinical practice, to identify intractability at an early therapeutic stage. In turn, this will facilitate patient management and stimulate the development of more effective therapeutic strategies, reducing the medicosocial and economic burden of intractable epilepsy.

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Conflicts of interest

All authors declare no conflict of interests. All authors had received financial support from a grant provided by the National Dutch Epilepsy Foundation for the submitted work. They had no financial relationship with any organization that might have an interest in the submitted work or relationships or activities that could appear to have influenced the submitted work.

Statement of ethical publication and ethical policy

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.

The work was carried out in accordance with the ''Uniform requirements for manuscripts submitted to Biomedical journals''.

Contributions

Merel Wassenaar (MSc): design or conceptualization of the study, analysis and interpretation of the data, drafting manuscript. Frans SS Leijten (MD, PhD): design or conceptualization of the study, revising the manuscript for intellectual content. Toine CG Egberts (PhD): revising the manuscript for intellectual content. Karel GM Moons (PhD): revising the manuscript for intellectual content. Sabine G Uijl (PhD): design or conceptualization of the study, analysis and interpretation of the data, revising the manuscript for intellectual content.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2013.06.013.

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