The natural history of epilepsy: an epidemiological view

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Better information of the natural history of epilepsy has important implications for understanding the underlying neurobiology, evaluating treatment strategies, and planning healthcare resources. The traditional pessimistic view has been dispelled by results from modern community based prospective studies, showing that over 60% of newly diagnosed patients will enter remission upon treatment. Recent outcome studies suggest that medical intractability may be predicted after failure of two antiepileptic drugs. Poor prognostic factors include a high initial seizure density, symptomatic aetiology, and presence of structural cerebral abnormalities, all of which can be identified early on. Among patients who have entered remission, many will remain seizure-free after antiepileptic drug treatment is withdrawn, suggesting that the underlying seizure generating factor has remitted. Whether some of these patients have entered remission "spontaneously" is contentious because, with effective pharmacotherapy for epilepsy in use for over 100 years, the natural history of untreated epilepsy is largely unknown. Circumstantial evidence, mostly arising from resource poor countries where antiepileptic drug treatment is not readily available, indicates that spontaneous remission may occur in up to 30% of cases. Observations from these complementary sources suggest that, at the population level, prognosis of newly diagnosed epilepsy may be broadly categorised into three groups: remission without treatment, remission with treatment only, and persistent seizures despite treatment. As understanding of the prognostic factors improves, the potential of a "prognostic group specific" management approach should be explored so that effective treatments may be used in a more rational and targeted fashion.

anticipated in any given case". Despite the availability of effective pharmacotherapy, heralded by the emergence of phenobarbital in 1912, Gowers's gloomy view was echoed by generations of researchers. For instance, in a survey in 1968, Rodin concluded that only 30% of patients with epilepsy ever achieved a two year remission.⁶ These studies, however, were small scale, hospital based, and retrospective. Results from recent prospective long term outcome studies have suggested a more favourable picture and greatly improved our understanding of the prognosis of epilepsy in response to treatment. In addition, epidemiological surveys from resource poor countries where anti-epileptic drug treatment is not readily available have shed important light on the course of untreated epilepsy.

We aim to provide an epidemiological interpretation of the evidence from these complementary sources of the "natural history" of epilepsy. Before the evidence is reviewed, it is important to appraise its strengths and weaknesses so that conclusions may be drawn in the appropriate context.

SOURCES AND QUALITY OF EVIDENCE

Epidemiology studies v drug trials

As antiepileptic drug treatment is usually started at the point of diagnosis in the industrialised world, outcome studies carried out in these countries mostly reflect the prognosis of treated epilepsy. The prerequisite for an accurate assessment of the prognosis of treated epilepsy is the inclusion of patients at the point of treatment initiation with prospective follow up. Modern data fulfilling this requirement may be derived from two main sources: epidemiological studies and monotherapy drug trials. Data from the former are preferred as the latter are primarily designed to establish the efficacy of the test compounds, in most cases to satisfy regulatory requirements. These trials tend to enrol highly selected patients, some previously treated, with a relatively short duration of follow up.⁷ For instance, in the two Veterans Administration (VA) studies (which were non-regulatory), 25% of the subjects were already on treatment at randomisation, most of them (approximately 90%) were male, and head trauma was the single most common cause of seizures.^{8,9} While the VA studies were pivotal in comparing the efficacy of the established antiepileptic drugs, results from such a selected sample of subjects clearly cannot be extrapolated to deduce the general outcome of epilepsy patients as a whole. In this review, we will not consider drug trials when evaluating the long term prognosis of treated epilepsy.

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It is increasingly recognised that, on an individual basis, the outcome of epilepsy strongly reflects the syndromic classification and underlying aetiology of the epilepsy.^{1–3} Consideration of the prognosis at population level, however, has important implications for the understanding of the underlying neurobiology, evaluation of treatment strategies, and planning of healthcare resources. Until very recently, the prognosis of epilepsy had been viewed with pessimism. Hippocrates believed that seizures beginning in adulthood lasted until death.⁴ Gowers⁵ conceded that "the spontaneous cessation of seizures is an event too rare to be

Community v centre based

There have been several prospective epidemiological studies addressing the outcome of epilepsy in various settings, including specialist centres and primary care clinics in the community (table 1). Each of these settings has its advantages and disadvantages. Compared with the latter, studies done in the former can be expected to have a higher degree of diagnostic accuracy and consistency in treatment approach. However, referral bias can be of major concern in centre based studies; this can be rectified by the inclusion of patient cohorts that are as unselected as possible.¹⁶ As the diagnosis of epilepsy generally requires specialist assessment,¹⁷ community based studies at the primary care level may suffer from case ascertainment error. In some population based studies, diagnostic error was minimised by case note review by expert panels.¹³ Representative population based and centre based studies will both be considered in this review.

Changes in definitions and treatment strategy over time

The classification schemes of seizures and epilepsies currently in use were proposed in 1981 and 1989, respectively.^{18, 19} Direct comparison between studies carried out before these schemes were widely adopted and the more recent ones could raise problems when analysing the effect of seizure type and epilepsy syndrome on prognosis. Additional methodological concerns in studies of long follow up duration may occur because the number of antiepileptic drugs available has increased dramatically over the past two decades while the time for initiating treatment has generally been delayed from the first seizure to at least the second attack.²⁰ The preferred treatment approach for newly diagnosed patients has also changed from polytherapy to monotherapy since the late 1970s/early 1980s. However, such concerns are likely to be ill founded as there is no evidence to support the view that these changes in treatment strategy have made a significant impact on the long term prognosis of epilepsy. Available human data suggest that, while antiepileptic drugs are effective in suppressing seizures, they do not alter the underlying epileptogenic process.^{21, 22}

Resource-poor countries

In contrast to the industrialised countries, antiepileptic drug treatment is not widely available in resource-poor countries, for various reasons. Indeed, it is estimated that 85% of epilepsy sufferers living in resource-poor countries do not receive any treatment.^{23–25} Epidemiologists have capitalised on the large proportion of untreated patients in this setting to study the “true” natural history of epilepsy.²⁶ It is important, however, to note the circumstantial nature of the evidence gathered in these retrospective surveys. In addition, case definitions used might not conform to international guidelines and, owing to lack of investigational procedures, classification is almost entirely semiological. Therefore, results from these studies should not be used to derive firm

conclusions but are best regarded as a basis for hypothesis generation.

REMISSION OF TREATED EPILEPSY

The first series of studies that provided a more accurate and positive assessment of the natural history of treated epilepsy was a community based project carried out in Rochester, Minnesota, USA. In this retrospective study, patients were identified from the Mayo Clinic record linkage system which included all medical contacts of residents of Olmsted County, Minnesota, since 1935.²⁷ Results primarily concerning the incidence, prevalence, and causes of seizures and epilepsy have been published in a series of reports, covering the periods from 1935 to 1967,²⁸ 1940 to 1980,²⁹ 1935 to 1984,³⁰ 1980 to 1984,³¹ and as summary articles for the 50 year period.^{27, 32} The issues of remission and early prognostic factors were explored in two reports.^{11, 33} In the initial examination, the probability of being in remission for five years at 20 years after diagnosis (that is, terminal remission) was 70%.³³ This was revised to 75% in the more recent analysis.¹¹ Predictors of a better outcome were absence of early life brain damage, absence of generalised epileptiform activity on EEG, and no history of generalised tonic-clonic seizures. The predictive value of these factors, however, was weak.¹¹

The National General Practice Study of Epilepsy (NGPSE) conducted in the United Kingdom is the largest ongoing prospective community based study of the prognosis of epileptic seizures.^{34–36} Patients with newly diagnosed confirmed or suspected epilepsy were identified from 275 general practices throughout the UK between 1984 and 1987. Cumulative remission rates—that is, actuarial estimates of percentage seizure-free at any time during follow up—and terminal remission rates for various durations at various time intervals were calculated. At a median follow up of 7.1 years, among the 564 patients with “definite” epilepsy, the chance of ever achieving five year remission after nine years from diagnosis was 68%, and 54% of patients were in five year terminal remission.¹³ Even when patients with acute symptomatic seizures and those who had only one seizure were excluded, 60% had achieved a five year remission by nine years of follow up.³⁷ Analysis of prognostic factors showed that only the number of seizures occurring in the first six months after presentation predicted the chance of remission.³⁸ The higher the “seizure density” within this initial phase of the seizure disorder, the less likely was it for the patients to enter remission. Other modern large scale studies that include only newly diagnosed patients followed up for long periods also tend to suggest a remission rate of 60–80% (table 1).

OUTCOME WITH RESPECT TO TREATMENT COURSE

These studies have provided a more accurate estimation of the probability of long term remission in relation to time from diagnosis; analysis of prognostic factors was, however,

Table 1 Terminal remission data from selected studies

Reference	Study setting	Special study features	No of patients	Median follow up (years)	Years in remission	% in remission at median follow up
Elwes <i>et al</i> ¹⁰	Hospital		106	5.5	2	79
Shafer <i>et al</i> ¹¹	Community		432	17	5	66
Collaborative Group ¹²	Hospital		280	4	1	70
Cockerell <i>et al</i> ¹³	Community	Definite epilepsy	564	7	5	68
Sillanpaa <i>et al</i> ¹⁴	Hospital	Children only	176	28	1	80
Lindsten <i>et al</i> ¹⁵	Community	≥1 baseline seizure	107	9	5	64
		≥2 baseline seizures	89	9	5	58

often undertaken irrespective of treatment status. None specifically addressed the relation between outcome and the course of antiepileptic drug treatment—that is, examining outcome with “drug treatment regimens” as the variable instead of “time”. Undoubtedly, it is important to the patient to know the likelihood of seizure freedom at various time points after the onset of seizures or diagnosis. However, the great majority of patients, at least in the developed countries, are started on antiepileptic drug treatment when a diagnosis of epilepsy is made. From a practical point of view, it would also be useful to gauge the chance of success with the first antiepileptic drug chosen as well as that of any successive regimens if it fails. When the first drug fails to control the epilepsy, as is often the case, little is known about the proportion of patients responding to subsequent monotherapy or combination treatment, and whether there is any difference in efficacy between these two treatment strategies. Such poor documentation of progress in response to treatment has resulted in confusion and lack of consensus over the definition of “refractory” epilepsy^{39, 40} and has hindered the development of a rational approach to management.

The relation between outcome and course of antiepileptic drug treatment has been examined specifically in an ongoing long term study of newly diagnosed patients conducted in Glasgow, Scotland, since 1982. In the first analysis reported in 2000, 525 unselected adolescent and adult patients with a new diagnosis of epilepsy were started on antiepileptic drug treatment and followed for up to 16 years (median five years).¹⁶ Among the 470 patients who had never previously received antiepileptic drug treatment, 64% entered terminal remission of at least one year. Response to the first antiepileptic drug was the most powerful predictor of prognosis. Among the 248 patients in whom the first drug was unsuccessful, only 79 (32%) subsequently became seizure-free. Indeed, only 11% of the 113 patients in whom the first drug failed primarily because of lack of efficacy (as opposed to adverse events or other causes) later became seizure-free. The predictability of “failure of first antiepileptic drug trial” for future refractory epilepsy has also been demonstrated in a retrospective study of children with temporal lobe epilepsy.⁴¹

When the outcome in response to treatment course was examined in the Glasgow study, it was found that 47% of patients became and remained seizure-free on the first drug, 13% on the second drug, but only 4% on the third drug or a combination of two drugs¹⁶ (table 2). Thirty five patients (7% of the total population) who responded to the first or second monotherapy were able to withdraw from treatment and remained seizure-free. In a follow up analysis it was shown that, of those who became seizure-free on the first drug, over 90% did so on relatively moderate dosing (daily doses of 800 mg or less of carbamazepine, 1500 mg or less of sodium valproate, and 300 mg or less of lamotrigine).⁴²

Results from the Glasgow studies support the hypothesis that patients with newly diagnosed epilepsy comprise two distinct populations which can be identified early in the

course of the treatment paradigm.⁴³ Around 60% of patients have a good prognosis. They will become seizure-free on a modest or moderate dose of the first or second choice antiepileptic drug as monotherapy without developing intolerable side effects. In some patients, the antiepileptic drug may subsequently be withdrawn without relapse of seizures, suggesting that the underlying seizure generating factor has indeed remitted. The hypothesis that newly diagnosed patients may comprise two distinct populations *de novo* is supported by recent pharmacogenetic data demonstrating that certain genetic variants may be associated with medical intractability⁴⁴ or even with the outcome of epilepsy surgery.⁴⁵

REMISSION AFTER SUBSEQUENT DRUG WITHDRAWAL

Whether, and to what extent, treatment can be successfully withdrawn in patients who have become seizure-free on antiepileptic drug treatment has been examined in several retrospective and prospective studies including both paediatric and adult patient populations.⁴⁶ Using specific methodological criteria, Berg and Shinnar⁴⁷ systematically reviewed 25 reports and concluded that the typical estimate of risk of relapse was 25% at one year after initiating antiepileptic drug withdrawal and 29% at two years. However, these studies probably suffered from significant selection bias and might have underestimated the relapse rate as many were small scale and retrospective, and all but one were uncontrolled. In addition, although estimating the risk of relapse after initiating (not completing) the discontinuation of antiepileptic drugs is of practical value, the meta-analysis did not address the actual proportion of patients able to remain seizure-free after complete withdrawal of treatment, which suggests remission of the underlying seizure generating factor.

The only large scale randomised controlled trial to compare the policies of continued antiepileptic drug treatment versus slow discontinuation of treatment is the multicentre MRC Antiepileptic Drug Withdrawal Study conducted in the United Kingdom.⁴⁸ Even in this large study, there was substantial self selection on the part of the patients, with 776 eligible subjects refusing to be randomised, the most important reason being possession of a driving licence. One thousand and thirteen patients who had been seizure-free for at least two years (median three years) were randomised to either policy, and followed up for between one and five years. Complete discontinuation was achieved in 373 patients (73%) in the slow withdrawal group. Among these, 260 (70%) remained in remission.

Combining the data from these pivotal studies, it could be inferred that, at a conservative estimate, at least 60% of newly diagnosed patients will enter long term remission on treatment initiation. Of these, 70% will be able to withdraw from antiepileptic drugs, and 70% of these will remain seizure-free. Thus, in approximately 30% (70% of 70% of 60%) of newly diagnosed patients, after receiving antiepileptic drug treatment of variable duration, the epileptogenic factor will eventually cease to exist or function.

SPONTANEOUS REMISSION?

It is widely accepted that the currently available antiepileptic drugs are anti-seizure rather than anti-epileptogenic—that is, they are effective in suppressing the symptoms (seizures) but they do not alter the underlying disease process (epileptogenesis) or its long term prognosis.^{21, 22} Although an anti-epileptogenic or disease modifying effect has been noted for some antiepileptic drugs in selected animal models,^{49, 50} such an effect has not been found in clinical trials. Results of antiepileptic drug prophylaxis studies among patients with febrile seizures,^{51, 52} severe head injury,^{53, 54} and craniotomy⁵⁵

Table 2 Success of antiepileptic drug regimens in 470 patients with newly diagnosed previously untreated epilepsy

Variable	n	%
Seizure-free on first monotherapy	222	47
Seizure-free on second monotherapy	61	13
Seizure-free on third monotherapy	6	1
Seizure-free on two drugs	12	3
Total seizure-free	301	64

Data taken from Kwan and Brodie, 2000.¹⁶

suggest that, despite suppressing immediate seizures, prophylactic antiepileptic drug treatment does not reduce the risk of the development of epilepsy in the long term.

Early treatment with antiepileptic drugs does not seem to improve long term prognosis either.⁵⁶ In the Italian FIRST study, 419 patients were randomised to immediate antiepileptic drug treatment after the first generalised tonic-clonic seizure or to delayed treatment initiation until a recurrence had occurred. Although the likelihood of seizure relapse was lower in the former group, both groups had the same time dependent probability of one and two year remission after starting treatment.⁵⁷ In a community based study in Kenya, 249 untreated patients completed a treatment programme with either carbamazepine or phenobarbital monotherapy for 12 months.⁵⁸ Although 53% of the patients had had recurrent seizures for over five years and 68% had had more than 10 seizures in the year before recruitment, altogether 53% were seizure-free in the last six months of treatment. There was no association between the remission rate and either the duration of epilepsy or the total number of lifetime seizures in this cohort.

It is therefore possible that among the 30% of newly diagnosed patients who are able to remain in remission after eventual drug withdrawal, the epileptogenic process has remitted spontaneously, regardless of treatment. Although this is an important issue with far reaching implications for the understanding of the neurobiology of epilepsy and for the valid interpretation of antiepileptic drug trials, the possibility of spontaneous remission of epilepsy has attracted relatively little attention from researchers.¹ This is probably because of ethical concerns about conducting a scientifically valid study to test this hypothesis. The true spontaneous remission rate can only be ascertained accurately by randomly assigning newly diagnosed patients to treatment or no treatment; such a protocol is difficult to justify ethically, as effective treatment has been available since 1857 and, in developed countries, antiepileptic drug treatment is usually begun immediately after diagnosis. Current evidence on the natural history of untreated epilepsy is therefore circumstantial, mostly emerging from resource-poor countries where treatment is not widely available.

NATURAL HISTORY OF UNTREATED EPILEPSY

A household survey in the highlands of northern Ecuador in the late 1980s identified 1029 people with a probable or definite history of epilepsy, 11% of whom had had a single episode.^{59–60} Among the 643 patients who had never received antiepileptic drug treatment, 314 (49%) had been seizure-free for at least the previous 12 months. Thus 31% of the whole patient population had entered remission spontaneously. Even this was likely to be an underestimation because, in population surveys, people whose epilepsy is in remission are more likely to be missed than those with active epilepsy.

Another piece of evidence suggesting that spontaneous remission of epilepsy occurs in a substantial proportion of patients is the similar prevalence rates in resource-poor and developed countries. This is despite the fact that many patients in the former have never received antiepileptic drug treatment.²⁶ A recent WHO commissioned household survey in rural regions of China identified 387 patients with definite epilepsy among 55 616 inhabitants.⁶¹ The prevalence rate of 7/1000 is comparable with those of developed countries.²⁶ Of those with active epilepsy, 63% were not under treatment ("treatment gap"), and of the 130 patients with inactive epilepsy, 41% had never been treated. It has been argued that the similar prevalence rates in resource-poor and developed nations partly reflects the higher mortality of epilepsy and shorter life expectancy in the former countries, but the average life expectancy of the Chinese population reached

Figure 1 Natural history of newly diagnosed epilepsy.

71.2 years in 2001.⁶² It is more likely that the main reason is the occurrence of spontaneous remission in many untreated cases.

It may be argued that data from resource-poor countries may not apply to the developed world because the aetiology of epilepsy may be different. In a Finnish study, 33 patients were retrospectively identified at a teaching hospital who had presented with two or more unprovoked seizures for which they had never received antiepileptic drug treatment, and it was found that 42% had entered a two year remission by 10 years after onset.⁶³ The study was limited by its small sample size and the likely bias that, in developed countries where treatment is readily available, patients with mild disease are more inclined to reject treatment. Nevertheless, the study showed that spontaneous remission of epilepsy has also been observed in developed countries.

AN EPIDEMIOLOGICAL INTERPRETATION

Observations from the above studies lend support to the suggestion that, at population level, prognosis of newly diagnosed epilepsy may be broadly categorised into three groups, reflecting the underlying neurobiological process (fig 1).

Group 1. Excellent prognosis—In 20–30% patients, the condition enters long term remission after a variable period of time and level of activity, probably even without antiepileptic drug treatment. If treated, these patients become seizure-free on the first or second monotherapy, often requiring no more than moderate doses, which can be successfully withdrawn after a period of seizure freedom. The primary aim of antiepileptic drug treatment, if indicated, in this group of patients is to suppress seizures until "spontaneous" remission occurs, as seizures themselves are not benign and may cause considerable morbidity or even mortality. Epilepsy syndromes that fall into this category include benign neonatal seizures, benign rolandic epilepsy, and childhood absence epilepsy.

Group 2. Remission with treatment only—The 20–30% of patients comprising the second group become, and remain, seizure-free only with continuing antiepileptic drug treatment. Some may require more than one antiepileptic drug and multiple attempts may be needed to find the right combination for the individual patient. The epileptogenic process does not truly remit and seizures recur if treatment is withdrawn. Continuing antiepileptic drug treatment is required to suppress seizure relapse. Examples of this group may include juvenile myoclonic epilepsy, and the bulk of the localisation related epilepsies.

Group 3. Continuing seizures despite treatment—In the remaining 30–40% of patients, seizures recur in varying degrees of intensity and frequency despite antiepileptic drug treatment. Some patients have frequent debilitating seizures qualifying as having “refractory” epilepsy.⁶⁴ Antiepileptic drug treatment can, at best, only ameliorate the severity or frequency of seizures. Conditions in this category include many symptomatic/cryptogenic localisation related epilepsies such as those associated with mesial temporal sclerosis, cortical dysplasia, gross structural brain lesions, the progressive myoclonic epilepsies, and West syndrome.

In practice, subgroups may be observed within these three broad categories. For instance, among patients belonging to the first prognostic group, although many enter remission “spontaneously”, some seem to need a small, often starting dose of an antiepileptic drug, and do not have another seizure after receiving the first dose of their first ever antiepileptic drug.^{65–66} Patients in the second prognostic group may also be further subdivided into those who remain seizure-free on monotherapy, and those who require several attempts of antiepileptic drug combinations before the “right” regimen is found.

It should be emphasised that, at the individual level, the natural history of epilepsy may be highly variable, depending upon the underlying syndromic classification and aetiology. A notable example is mesial temporal lobe epilepsy associated with hippocampal sclerosis, for which growing evidence suggests a progressive course in some patients.^{67–68} Accumulating data, mostly derived from histopathological⁶⁹ and imaging models⁷⁰ of temporal lobe epilepsy, suggest that recurrent seizures may induce long lasting neuronal injury. It remains to be seen whether these neuronal changes actually result in perpetuating seizures. In a retrospective survey of 333 patients who underwent resective surgery for medically refractory epilepsy (88% had anterior temporal lobectomy), the average time to failure of two first line antiepileptic drugs was 9.1 years (median five years). Twenty six per cent of 284 patients from the cohort recalled a previous period of at least one year seizure freedom since the onset of epilepsy.⁷¹ This suggests that for some patients with temporal lobe epilepsy, medical intractability may not declare itself in the early stage of the disorder. Clearly, as epilepsy is not a single disease, syndrome/aetiology specific prospective prognostic studies are needed if we are to manage individual patients in a more rational fashion.

IMPLICATIONS FOR CLINICAL RESEARCH PARADIGM

This conceptual framework has important implications for the formulation of a “prognostic group based” approach to the management of newly diagnosed epilepsy. With few exceptions, the established and newer antiepileptic drugs have shown similar efficacy in comparative monotherapy studies recruiting newly diagnosed patients.⁷ The difficulty in finding differences in efficacy among the various antiepileptic drugs for these patients might be partly explained by the spontaneous remission in a substantial proportion of cases. Targeting those with a probable poorer prognosis might increase the chance of detecting differences in efficacy in a head to head monotherapy trial.

With mounting circumstantial evidence of eventual spontaneous remission in a substantial proportion of newly diagnosed patients, the objections on ethical grounds to conducting randomised placebo controlled trials in this patient population may require re-evaluation. It could be argued that routine prescription of antiepileptic drugs, with a catalogue of potential side effects,⁷² to the many newly diagnosed patients who may enter remission spontaneously raises ethical concern. This applies particularly to those

without poor prognostic factors—that is, those without structural brain abnormalities, high initial seizure density, or abnormal EEG findings.^{16–38–39} Targeting these patients in a placebo controlled study would minimise the risk of recurrent seizures.

CONCLUSIONS

The natural history of epilepsy remains poorly understood. Complementary data from developed and resource-poor countries suggest that spontaneous remission occurs in a substantial proportion of patients. While seizures may be controlled by antiepileptic drug treatment in some patients, others remain refractory to medical treatment. Accumulating evidence supports the suggestion that, at the population level, newly diagnosed patients may be categorised from onset into three broad groups of treatment outcome based on clinical characteristics. As our understanding of these prognostic factors improves, the potential of a “prognostic group specific” approach for the management of newly diagnosed epilepsy should be explored so that effective treatment may be used in a more rational and targeted fashion.⁷³

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