Changing view of prognosis of epilepsy

Getting better all the time

The older, pessimistic view of the prognosis of epilepsy was based on studies of patients with chronic epilepsy living in institutions or attending hospital clinics. Recently this has given way to a more optimistic perspective, based on studies of newly diagnosed epileptic patients both in the community and in hospital.¹

Studies of patients with chronic epilepsy

Gowers first applied a statistical approach to the prognosis of epilepsy in the late nineteenth century,² but the traditional gloomy view of prognosis was best summarised by Rodin, who reviewed studies from Gowers up to his own valuable work in the 1960s.³ Rodin concluded that only about a third of epileptic patients were likely to achieve a terminal remission of at least two years; that the longer patients were followed up the more likely they were to have a relapse; and that four fifths of all patients with epilepsy were likely to have a chronic seizure disorder. He regarded epilepsy as a chronic condition with remissions and exacerbations, but he also recognised that his review was based almost wholly on studies of patients with chronic disease living in institutions or attending special outpatient clinics. At the time of his review there had been no systematic study of epilepsy at its onset.

Another interesting feature of the period of almost a century reviewed by Rodin was the introduction and use of effective drugs, including bromides, barbiturates, hydantoins, succinimides, and carbamazepine—most of which are still widely prescribed today. Rodin questioned whether these had improved the overall prognosis over this time. But a factor that was and still is missing in our understanding of prognosis is information on the prognosis of untreated epilepsy. Practice was and perhaps still is influenced by Gowers's view that the spontaneous cessation of the disease was an event too rare to be reasonably expected.²

Studies of newly diagnosed patients

In the past decade new studies have focused on epilepsy as viewed and monitored from the onset of the disorder in both the community and the hospital clinic (table I). This has given new insight into the evolution of epilepsy, dispelled some gloomier ideas about prognosis based on studies of patients with chronic epilepsy, and raised fundamental questions about the nature and treatment of epilepsy.

TABLE I—Prognostic studies of patients with newly diagnosed epilepsy

Type of study	No of patients	Duration of remission (years)	Percentage in remission
Community (retrospective):			
Annegers <i>et al</i> ⁴	457	5	70
Goodridge and Shorvon ⁵	122	4	69
Hospital (retrospective):			
Okuma and Kumashiro ⁶	1868	3	58.3
Hospital (prospective):			
Elwes <i>et al</i> ⁷	106	2	82
Beghi and Tognoni ⁸	283	From treatment*	48

*Mean follow up 21.6 months.

Community based studies

The prevalence of active epilepsy varies from 4 to 10 in 1000 depending on definitions and methods of study.⁹ Goodridge and Shorvon found that the lifetime prevalence of epilepsy (excluding febrile convulsions but including single seizures) was 20.2 in 1000, whereas the prevalence of continuing active epilepsy was 5.3.⁵ Thus most patients probably do not develop chronic epilepsy. Annegers *et al* retrospectively reviewed the prognosis of 475 patients who had had an initial diagnosis of epilepsy recorded on the Mayo Clinic record linkage system during 1935-74.⁴ In contrast to Rodin's observations,³ remission rates improved with duration of follow up. Among those followed up for 20 years over two thirds were in five year remission and half had stopped taking drugs. Goodridge and Shorvon reviewed the general practice records of 6000 people in Kent, England, and found that of 122 patients identified with at least one non-febrile seizure (82% of which were recurrent) 69% had been in remission for four years at 15 years of follow up.⁵

Retrospective hospital based studies

In 1981 the Group for the Study of Prognosis of Epilepsy in Japan reported on the outcome of 1868 patients with epilepsy who had been seen at 20 university hospital clinics during 1964-7 at the onset of their disorder.⁶ The three year remission rate was 58% at 10 years of follow up, a much more favourable prognosis than had been described in any hospital population, no doubt due to including only newly diagnosed patients. Even so, this sample represented only 42% of the patients who had been seen in the clinics, and it was not clear how representative this subgroup was of the total population.

Prospective hospital based studies

Elwes *et al* prospectively studied 106 adolescent and adult patients with newly diagnosed, untreated, epilepsy referred to a district general hospital in London.⁷ Each patient had had at least two tonic-clonic or partial seizures, or both, in the past year. Treatment was with either phenytoin or carbamazepine, initially in a small dose. The serum drug concentrations were monitored regularly. If seizures recurred the dosage was increased, if necessary into the optimum blood concentration range. The median duration of follow up was 66 months. The overall prognosis for this population was good. Seventy three per cent had been in remission for one year by two years of follow up, 88% by four years, and 92% by eight years; the pattern for two year remission rates was similar, with 73% in two year remission by four years of follow up and 82% by eight years. Among 79 patients in whom seizures were controlled for two years, subsequent follow up data were available in 76. Twenty five had a recurrence of seizures, which consisted of only one or two attacks in 17 and was related to poor compliance in 16.

Beghi and Tognoni supervised a prospective study of prognosis in 283 children and adults in whom epilepsy was newly diagnosed from 14 centres in Italy.⁸ Fifty six per cent had generalised seizure disorders and 44% partial seizures with or without secondary generalisation. The patients were

given monotherapy with various drugs, but drug concentrations in the blood were not routinely monitored. The measure of prognosis was the first seizure after the onset of treatment. At a mean follow up of 21.6 months nearly half of the patients remained completely free of seizures. This good overall prognosis may have been influenced by the inclusion in the series of 51 patients who had had only a single seizure.

These prognostic findings are supported by several treatment studies in newly diagnosed patients, which showed good early control in 60-80% of patients treated with any of the main antiepileptic drugs used alone.^{1 10 11} Indeed, prospective comparative trials of the efficacy of several drugs (phenobarbitone, phenytoin, primidone, carbamazepine, and valproate) have not shown appreciable differences among the drugs for specific seizure types in newly diagnosed adults or children.¹²⁻¹⁶

Factors influencing prognosis

Both the older studies of patients with chronic epilepsy³ and more recent studies of newly diagnosed patients⁶⁻⁸ show that certain factors have an adverse influence on long term prognosis. These include partial or mixed seizure types (as compared with tonic-clonic seizures); symptomatic epilepsy; clinical or computed tomographic evidence of cerebral disease; and intellectual handicap, psychiatric illness, personality change, or social problems. Older age, a family history of epilepsy, and severe background or "epileptiform" abnormalities on electroencephalography are less certain indicators of a poorer prognosis.

The influence of early treatment

Gowers and Rodin both stated that the longer the history of epilepsy the less favourable the outcome.^{2 3} Elwes *et al* reported that even in the presence of adverse prognostic factors, most newly diagnosed patients entered one or two years' remission with treatment.⁷ The longer seizures continued after starting treatment, however, the lower the subsequent remission rate. Thus, if seizures were continuing two years after the start of treatment the subsequent one year remission rate was roughly halved. The first two years of treatment therefore seem to be crucial as most patients whose seizures are not controlled in this period go on to develop chronic epilepsy.

So is early effective treatment important to prevent the development of chronic epilepsy?^{1 17 18} Epilepsy may be viewed as a process in which each seizure facilitates the occurrence of another.^{2 17 19 20} Nevertheless, the more traditional view that patients who develop chronic drug resistant epilepsy simply have more "severe" epilepsy from the start is not excluded. Furthermore, some forms of epilepsy, especially in childhood—for example, petit mal or benign rolandic epilepsy—may undergo spontaneous remission.

The possible importance of early treatment is emphasised by recent studies suggesting that the long term prognosis is influenced by how many seizures have occurred before treatment. Beghi and Tognoni compared three groups of newly diagnosed patients: those with single seizures, between two and six seizures, and more than six seizures.⁸ The prognosis was poorer as the number of pretreatment seizures increased. In long term prospective studies in 241 newly diagnosed adults¹⁵ and 167 children¹⁶ the most important adverse prognostic factor was the number of tonic-clonic or partial seizures before treatment.²¹ The influence of the number of untreated seizures on later prognosis is in keeping with Gowers's view² and calls to mind the kindling model of epilepsy.²⁰

TABLE II—Prognostic studies of patients presenting with a single seizure

Author	No of patients	Length of follow up (months)	Rate of recurrence (%)
Thomas ²²	42	—	27
Johnson <i>et al</i> ²³	77	36	64
Saunders and Marshall ²⁴	33	26	64
Cleland <i>et al</i> ²⁵	70	57	39
Hauser <i>et al</i> ²⁶	244	36	27
Todt <i>et al</i> ²⁷	179	12	59
Camfield <i>et al</i> ²⁸	168	—	52
Elwes <i>et al</i> ²⁹	139	36	71
Annegers <i>et al</i> ³⁰	380	60	56
Hopkins <i>et al</i> ³¹	100	36	52

The single seizure

If early treatment for epilepsy is important should we treat single seizures? The prognosis of a single seizure is a controversial subject (table II²²⁻³¹), the recurrence rate varying from 27% to 71% at three years of follow up.

A multicentre study of 408 patients aged over 16 presenting to neurological departments confirmed that most single seizures are tonic-clonic attacks.³¹ Partial attacks are usually more frequent, may occur in clusters, and initially are often not recognised as seizures. They thus present to doctors as a single event more rarely. Several factors may have influenced the wide variation in the reported recurrence rates after a first attack: the age of the population studied, whether the study was retrospective or prospective, the types and causes of the seizures, and whether some of the patients were treated with antiepileptic drugs. The most important factor, however, is the time between the occurrence of the first seizure and presentation to a clinic where the patient is entered into the single seizure study. In one third of patients with established epilepsy the second attack follows the first within one month.^{2 32} Therefore if one month elapses before a patient with a first seizure is seen in a neurological clinic those with early recurrence will be selected out because they have already developed epilepsy.

In the study of patients with single seizures by Elwes *et al*, which had the highest rate of relapse (71%), all the 133 patients were identified within one day of the attack.²⁹ Only 103 of them, however, were still single seizure patients when they were seen in a neurological clinic within one month; their rate of relapse was 57%.³³ Similarly, Hopkins *et al* reported a rate of relapse of 52% in patients seen in neurological clinics within one week, but of only 22% in those seen after eight weeks.³¹ The recurrence rate of 39% described by Cleland *et al* was in patients seen at least six weeks after the event.²⁵ Epidemiological and general practice studies support the view that in most patients seizures are recurrent. In Rochester, Minnesota, only 23% of patients had a single seizure.³⁴ The corresponding figure from greater Aarhus, Denmark, was 16%.²⁵ In a general practice in Kent only 18% of seizures were isolated.⁵

Thus Gowers was probably right.² Overall there is a high rate of relapse after a single seizure, but for each patient the probability of recurrence falls in proportion to the time between the seizure and presentation to a hospital clinic. Early relapse results in patients presenting with epilepsy to neurologists or paediatricians. Whether the patient with a single attack should be treated with an antiepileptic drug has never been adequately investigated.³⁶

Natural course of untreated epilepsy

One of the main difficulties in evaluating the influence of antiepileptic treatment on prognosis is the lack of information about the natural course of untreated epilepsy. For obvious

ethical reasons no one has ever compared treatment with no treatment or a placebo in newly diagnosed epilepsy. Elwes *et al* attempted a limited study of the natural course of untreated epilepsy by retrospectively examining the pattern of occurrence of seizures in 183 patients with two to five tonic-clonic seizures newly referred to a neurological clinic.³² The median interval between the first two seizures was 12 weeks; between the second and third, eight; between the third and fourth, four; and between the fourth and fifth, three. Successive seizure intervals could be compared in 82 patients. In three fifths the interval decreased, in one fifth it did not change, and in one fifth it increased. As the authors pointed out, these data might have been biased by the study being retrospective and hospital based. Furthermore, such observations can relate only to the more dramatic and easily remembered tonic-clonic attacks and may not apply to partial or other forms of seizure. Ideally studies of the natural course of untreated epilepsy should be undertaken prospectively in the community, but these would obviously pose considerable practical and ethical difficulties. Nevertheless, such a general practice based study is underway in Britain (Y Hart *et al*, 18th epilepsy international congress, New Delhi, 1989).

The suggestion by Elwes *et al* that in many patients there is an accelerating process of epilepsy in the early stages is in keeping with the evidence linking the number of untreated seizures with longer term prognosis and again raises the question whether or not epilepsy should be treated early to prevent chronic epilepsy.

Conclusions

The recent studies of patients with newly diagnosed epilepsy have shown a more favourable prognosis than that reported from studies of patients with chronic epilepsy. Only about 20-30% of newly diagnosed patients develop chronic epilepsy. Similar factors adversely influence prognosis in patients with newly diagnosed and chronic epilepsy but apparently to a lesser extent in the newly diagnosed. These observations have raised questions about the nature and treatment of epilepsy.

Epilepsy has been viewed as a symptom, a syndrome (or syndromes), and an illness. An additional or alternative view is that it is a process, which changes its character over time. We know little about the natural course of untreated epilepsy, but there is evidence of an accelerating process in the early stages of the disorder in some patients with tonic-clonic seizures, perhaps by the mechanism proposed by Gowers. The longer term prognosis is influenced by the number of seizures before treatment. The results of treatment of newly diagnosed patients seem to be good, with high early control rates. But if seizures are not "arrested" (to use Gowers's terminology) within two years of the onset of the disorder and treatment there is a considerable risk of chronic drug resistant epilepsy. The contrast between the efficacy of the same drugs in newly diagnosed patients and those with chronic disease is striking. In the later stages of epilepsy new drugs or alternative treatments—for example, surgery—are needed. Gowers thought that the spontaneous remission of seizures was unusual, but this clearly occurs in some patients, especially perhaps in certain childhood disorders. The brain is after all the seat of competing excitatory and inhibitory processes and the latter may dominate.

This more dynamic longitudinal view of epilepsy has certain implications that require further study. Firstly, early effective treatment in the newly diagnosed patient may prevent the evolution of chronic drug resistant epilepsy. Studies of the effect of early versus delayed treatment strategies on longer term prognosis would shed light on this possibility, as well as on the natural course of untreated epilepsy. Secondly, if early treatment is important then we urgently require studies of the management of patients with a single unprovoked seizure. Thirdly, treatment strategies will need to vary according to the stage reached in the evolution of the disorder. Lastly, will antiepileptic drug treatment, in addition to suppressing seizures, increase the prospects for spontaneous remission?

E H REYNOLDS

Consultant Neurologist,
Maudsley and King's College Hospitals,
London SE5 9RS
(Correspondence to King's College Hospital)

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