The Early Treatment and Prognosis of Epilepsy

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Recent community- and hospital-based studies of epilepsy from its onset suggest a much better prognosis than previously recognized, with about three-quarters of patients entering long-term remission on current medication. The first two years of medication are crucial in determining longer-term prognosis. Early effective therapy may be important in preventing the evolution of chronic epilepsy. Adverse prognostic factors include brain lesions, neuropsychiatric handicaps, and poor compliance.

PROGNOSIS OF EPILEPSY

The traditional and rather gloomy view of prognosis was summarized in the detailed review by Rodin [1] which spans the period from Gowers [2], who first applied a statistical approach to prognosis in the late nineteenth century, to Rodin's own valuable studies. Rodin concluded that only approximately one-third of epileptic patients are likely to achieve a terminal remission of at least two years; that the longer patients are followed up, the more likely is relapse to occur; and that 80 percent of all patients with epilepsy are likely to have a chronic seizure disorder. Although the latter does not rule out short-term remissions, it emphasizes that epilepsy should be regarded as a chronic condition with remissions and exacerbations. Rodin recognized that his review was based almost wholly on studies of chronic patients in institutions or attending special outpatient clinics. He noted that the longer the history of epilepsy prior to hospital consultation the worse the prognosis, and he rightly drew attention to the good prognosis reported by Gowers [2] in patients with a short history of epilepsy treated with bromides. At the time of his review there had been no systematic study of epilepsy at its onset and, as Shorvon [3] has pointed out, a weakness or source of misunderstanding in the studies reviewed was a failure to appreciate certain temporal aspects of the development of epilepsy, arising from the retrospective, cross-sectional nature of the investigations, based on heterogeneous populations of patients with a very variable duration of illness. Another interesting feature of the period, approximately a century, reviewed by Rodin was the introduction and use of many major anticonvulsant drugs of undoubted efficacy, from bromides, through barbiturates, to hydantoins, succinamides, and carbamazepine, most of which are still widely prescribed today. Rodin questioned whether there had been any improvement in overall prognosis throughout this time. A factor which has been missing in our understanding of prognosis is any information about the prognosis of untreated epilepsy. Practice was and still is perhaps influenced by Gowers's [2] view that the spontaneous cessation of the disease was an event too rare to be reasonably anticipated in any given case.

In the last decade new studies have focused attention on epilepsy as viewed and

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followed from the onset of the disorder, both in the community and the hospital clinic. This has given some new insights into the temporal evolution of epilepsy, dispelled some of the gloomier views of prognosis based on studies of chronic patients, and raised some fundamental questions about the nature and treatment of epilepsy, which will be discussed in this review.

COMMUNITY-BASED STUDIES

Prevalence rates for active epilepsy vary from 4 to 10/1,000, depending on definitions and methods of study [4]. If, however, up to 5 percent of the general population may at some time experience a non-febrile seizure, as has been reported [5], this suggests that most of them do not go on to develop chronic epilepsy. In keeping with this, Goodridge and Shorvon [6] found that the lifetime prevalence of epilepsy (excluding febrile convulsions but including single seizures) was 20.2/1,000, whereas the prevalence of continuing “active” epilepsy was 5.3/1,000.

Annegers et al. [7] retrospectively reviewed the prognosis of 475 patients who had an initial diagnosis of epilepsy recorded on the Mayo Clinic record linkage system between 1935 and 1974. In contrast to Rodin’s observations, remission rates improved with duration of follow-up, and in those followed for 20 years as many as 70 percent were in five-year remission, and 50 percent had withdrawn medication. Goodridge and Shorvon [6] reviewed the general practice records of a population of 6,000 in Kent, U.K. Of 122 patients identified with at least one non-febrile seizure (82 percent of which were recurrent), 69 percent were in a four-year remission at 15 years of follow-up.

The much more favorable picture of prognosis emerging from these retrospective community-based studies is also supported by our own hospital-based studies of patients followed prospectively from the onset of their epilepsy over the last ten years.

PROSPECTIVE STUDY OF NEWLY DIAGNOSED EPILEPSY

In the past decade my colleagues and I have followed prospectively 106 adolescent or adult patients with newly diagnosed, previously untreated epilepsy referred to the neurology department at Kings College Hospital, a district general hospital in London [8,9]. Each patient had had at least two tonic clonic or partial seizures in the past year. Treatment was with monotherapy with either phenytoin (61 patients) or carbamazepine (45 patients), initially in a small dose. Serum levels of the drugs were monitored regularly. If seizures recurred the dosage was increased, if necessary into the optimum blood level range. The occurrence of two or more seizures despite an optimum serum level of phenytoin or carbamazepine was regarded as evidence of failure of monotherapy and a second drug was added. The median duration of follow-up was 66 months (range, 6–96 months).

The overall prognosis for this population was very good: 73 percent were in one-year remission by two years of follow-up, 88 percent by four years, and 92 percent by eight years; the pattern for two-year remission rates was similar with 73 percent in two-year remission by four years of follow-up and 82 percent by eight years. There were 79 patients in whom seizures were controlled for two years and subsequent follow-up data were available in 76; 51 percent remained completely seizure-free for the rest of follow-up; 25 had a recurrence of seizures, which consisted of only two attacks in 17 and was related to poor compliance in 16.
Factors Influencing Prognosis

A number of factors had an adverse effect on remission rates. These included partial as compared with tonic clonic seizures, a high frequency of tonic clonic seizures before treatment, a family history of seizures, and, most significantly, the presence of additional neurological, psychiatric, or social handicaps. In general these adverse prognostic factors are similar to those identified in studies of chronic patients [1]. Only 21 of our patients failed to respond to monotherapy, and none of them benefitted from the addition of a second drug. Interestingly, 19 of the monotherapy failures occurred within the first two years of treatment, and there were only two late failures. We compared the 21 treatment failures with 21 treatment responders out of the original population of 106, carefully matched for age, sex, seizure, and treatment variables [10]. Two factors emerged which were clearly associated with failure of monotherapy: poor compliance and the presence of cerebral pathology.

The Influence of Early Treatment

Even in the presence of adverse prognostic factors such as partial seizures and additional neuropsychiatric handicaps, the majority of our patients went into one- or two-year remission. It therefore seemed probable that other unidentified factors might contribute to treatment failure and a poor prognosis. One such possible factor which interests us is the influence of early treatment and response on later prognosis [8,9,11]. We have shown that the longer seizures continue after the onset of treatment the less likely is the patient to go into remission. Thus for the patient still having seizures two years after the onset of treatment the subsequent one-year remission rate is approximately halved. The first two years of treatment are very important in relation to longer-term prognosis, and it is interesting that all our patients who failed to respond to optimum single-drug therapy within this period went on to develop chronic epilepsy.

This data is open to two possible interpretations [11]. First, perhaps, those patients who fail to go into remission and develop chronic epilepsy have inherently more "severe" epilepsy, so "severe" that they cannot be controlled by currently available medication. The concept of "severe" epilepsy, however, especially in a patient presenting with his or her first few seizures, is a difficult one, the clarification of which would require prolonged observation of untreated patients, which for ethical reasons is unlikely to be undertaken. Furthermore, there is little doubt that in many individual patients epilepsy may appear to be either "severe" or "mild" at different times. An alternative explanation which I prefer is to regard epilepsy as a process in which there are less apparent cerebral events between the visible seizures and which may remit spontaneously or under the influence of anticonvulsant treatment. That remission is not always simply a matter of drug treatment is illustrated by the well-known tendency for some seizure types, such as petit mal or certain benign epilepsies of childhood, to remit spontaneously. In chronic epilepsy, this process evolves erratically or progressively out of control, such that it becomes unresponsive to currently available medication.

One mechanism which might underlie the evolution of chronic epilepsy was suggested by Gowers a century ago. He commented that "when one attack has occurred, whether in apparent consequence of an immediate excitant or not, others usually follow without any immediate traceable cause. The effect of a convulsion on the nerve centres is such as to render the occurrence of another more easy, to intensify the predisposition that already exists. Thus every fit may be said to be, in part, the
result of those which have preceded it, the cause of those which follow it." He presented evidence from his own careful observations that the prognosis for seizure control was inversely proportional to the duration of the disorder. He emphasized the very favorable prognosis in patients with a seizure disorder of less than one year (83 percent "arrested") and the relatively high probability that seizures would not be controlled if the disorder had been present for more than five years. Shorvon [3] has summarized other recent studies of monotherapy with currently available drugs in relatively smaller numbers of newly diagnosed epileptic patients followed up for no more than two years, which have confirmed the good prognosis in such patients.

Other possible evidence in favor of an evolving process of epilepsy has come from an analysis of the time intervals between attacks in those patients presenting to us at a neurological clinic with three or more untreated tonic clonic seizures [12]. There is a remarkable decline in the interval between successive seizures which we observe in the vast majority of such referrals. The data is retrospective, however, and it is possible that patients with lengthening intervals between seizures are less likely to be referred to hospital. On the other hand, Goodridge and Shorvon [6] found that the great majority of patients with newly diagnosed epilepsy are referred to hospital.

The possible implication of our studies and those of Gowers [2] is that the process of epilepsy should be treated early and effectively to prevent the development of chronic epilepsy [11]. Once chronic epilepsy is established, especially after the first two years, it becomes very difficult to treat.

CONCLUSIONS

Recent retrospective community-based studies and our own hospital-based prospective studies of newly diagnosed epileptic patients over the last ten years suggest that the overall prognosis for epilepsy is much more favorable than has been implied from previous hospital- and institution-based investigations. The unduly gloomy view of prognosis which emerged from the latter studies was due to the accumulation of chronic patients in such clinics. In fact, some three-quarters of new, previously untreated referrals can expect to be controlled by currently available medication. As epilepsy is so common, the approximately 25 percent of patients who go on to develop chronic epilepsy still represent an enormous burden on and challenge to Health Services, as chronic epilepsy is so difficult to treat.

The first two years of treatment are crucial, and most patients who go on to develop chronic epilepsy can be identified within this period. Factors which contribute to failure of treatment and the evolution of chronic epilepsy are the presence of brain lesions and neuropsychiatric handicaps, and especially poor compliance. In addition, there is some evidence to suggest that epilepsy should be regarded as a process, which in many patients has a tendency to escalate, perhaps by the mechanism proposed by Gowers, unless arrested by treatment. Early effective treatment associated with good compliance may thus be important in the prevention of chronic epilepsy.

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