Chapter 1

The Natural History of Epilepsy

Byungin Lee and Sung-Eun Kim

Natural History of Untreated Epilepsy

Understanding the natural course of epilepsy influences the advice given to patients, the treatment strategies and the timing of referral for surgery-based treatments. As such, it is integral to clinical care. The natural course of epilepsy at population level also has important implications for understanding the underlying neurobiology and for developing means for epilepsy prevention, new treatments and allocation of healthcare resources.

However, an understanding of the natural history or course of epilepsy depends upon knowing the clinical manifestations of epilepsy without treatment or other intervention from the time of onset until disease resolution or death, and such studies are unethical when treatment is available and requested by patients. One approach to such studies uses epidemiological studies in developing countries where patients with epilepsy are not offered any treatment throughout their illness. However, differences in aetiology, diagnostic accuracy and environmental factors need to be considered before generalization of the results.

A household survey in northern Ecuador identified 1029 patients with epilepsy and found a high rate of disease inactivity; 44% of all patients were seizure-free during the preceding 12 months, despite 70% never receiving anti-seizure medication (ASM) [1]. In this study, the lifetime prevalence (19.5/1000) and incidence (190/100 000/year) of epilepsy were much higher than other nations, but the prevalence of active epilepsy (8/1000) was comparable. A WHO-commissioned household survey in a rural region of China identified an epilepsy prevalence rate of 7/1000, which is comparable to developed countries, and 63% of 257 patients with active epilepsy were not receiving treatment, whereas 41% of the 130 patients with inactive epilepsy had never been treated [2]. A longitudinal study of 103 patients who were diagnosed with active epilepsy but not treated with an ASM was conducted in Bolivia [3]. After 10 years of follow-up, 31 of the 71 patients (44%) with seizure occurrence information were seizure-free for longer than five years. If the study included all 103 patients of the original cohort in the denominator, the spontaneous remission rate would be 30%, if all who were lost to follow-up continued to experience seizures.

The prevalence of epilepsy is dependent on both epilepsy incidence and duration. Based on a prevalence of 5 per 1000 and incidence of 50 per 100 000 per year, the expected average duration of active epilepsy should be around 10 years [4], which implies that a significant proportion of patients eventually achieve spontaneous remission. However, this average duration would be impacted by the already recognized self-limited epilepsies of childhood and mortality in older adults from other causes. The incidence of epilepsy is generally higher in developing countries, while prevalence of active epilepsy is approximately equal throughout the world. Although there has been a speculation about higher premature mortality in developing countries, a high spontaneous remission rate of epilepsy (30–40%) among incident cases seems to be an important contribution to the higher incidence and comparable prevalence, assuming diagnostic accuracy is comparable to developed countries [5].

Natural History of Treated Epilepsy

ASM treatment is usually started at the time of diagnosis in the developed world, and outcome studies carried out in these countries mostly reflect the prognosis of treated epilepsy. Accurate assessment of treated epilepsy is best achieved by prospective follow-up of newly diagnosed patients at the point of treatment initiation. In a Rochester, Minnesota study, five-year remission (5-YR) rates were 65% at 10 years and 76% at 20 years after diagnosis [6]; 70% of patients achieved five-year terminal remission (5-YTR) with 50% being off ASMs (Figure 1.1). Favourable predictors were idiopathic/cryptogenic aetiology,

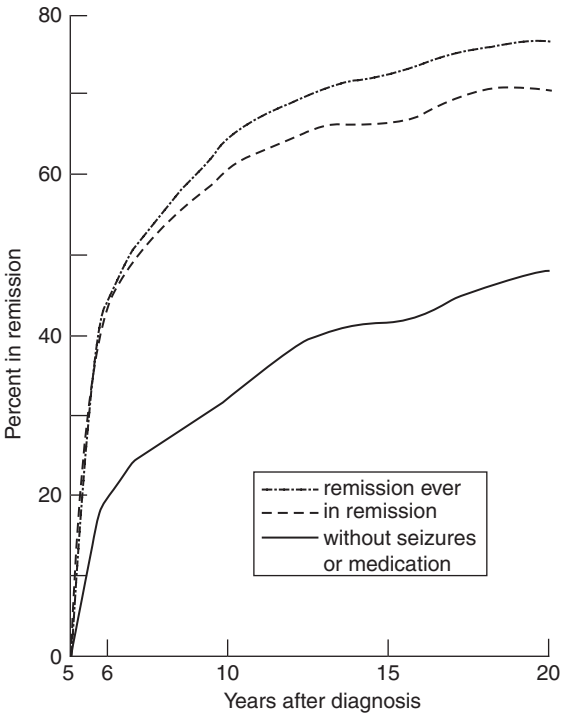

Figure 1.1 Time-dependent five-year remission rates among 457 patients with newly diagnosed epilepsy in Rochester study (with permission from [6])

Remission ever: percentage of patients who achieved five-year remission status.

In remission: percentage who have been seizure-free during the last five years or more.

Without seizures or medication: percentage of patients who were seizure-free off medication during the last five years

generalized tonic-clonic seizures (GTCS), and age of onset before age 10 years. In comparison, a community-based study in Kenya of ASM treatment on the natural course of epilepsy showed that either carbamazepine or phenobarbital therapy in patients with chronic epilepsies resulted in 53% seizure freedom at 12 months of treatment [7]. As such, a similar outcome was observed in a developing country, which supports comparability between developing and developed countries. In the Kenya study, there was no association between the remission rate and either the duration of epilepsy or the total number of lifetime seizures before treatment, suggesting that the impact of current ASM treatment on the natural course of epilepsy is probably not significant.

The National General Practice Study of Epilepsy (NGPSE) from the United Kingdom is a prospective community-based study of 564 patients with definite epileptic seizures [8]. Chances of achieving 3-YR and 5-YR at nine years of follow-up were 86% and 68%, respectively. After 25 years of follow-up, 82% of 327 patients with definite epilepsy achieved 5-YTR [9]. Analysis of seizure patterns showed that 27% had early seizure remission continuing to 5-YTR, while 8% had continuous seizure recurrences without having any 1-YR. Late terminal remission was achieved in 22% of patients and the remaining patients had complex patterns of alternating 'remission and relapse'.

Response to sequential ASM trials on the clinical course in adults with newly diagnosed epilepsy were investigated in a hospital-based cohort [10–13]. Among 1098 newly diagnosed patients, 68% achieved at least 1-YTR by 7.5 years of follow-up. Successful response to the first drug regimen was achieved in 49.5%, 36.7% to the second drug, and 12% to 24% in response to the third or subsequent drugs [13]. The clinical courses of newly diagnosed people with epilepsy (PWE) were classified into four patterns: 'early and sustained seizure freedom' was achieved in 37%, 'delayed but sustained seizure freedom' in 22%, alternating periods of 'remission and relapse' in 16% and no achievement of 1–YR ever in 25%.

Several long-term paediatric cohort studies provided further insights into the natural course of childhood-onset epilepsy. A Finnish paediatric cohort included 245 patients (150 incident and 95 prevalent cases) under the age of 16 years in 1964 [14]. At 37 years of follow-up for 144 incident cases, 67% of patients were in 5-YTR on or off ASMs. Early remission, starting within the first year of treatment, was seen in 45 (32%) patients and 23 (16%) of them maintained remission until the end of follow-up without any relapse. Late remission with a mean delay of nine years was achieved by 72 (50%), and 46 (32%) achieved 5-YTR without any relapse. Following a relapse after early or late remission, 28 (19%) patients achieved 5-YTR, indicating a 'remission-relapse' pattern and 20 (14%) patients did not re-enter remission, indicating a worsening course of epilepsy. Twenty-seven (19%) patients failed to achieve any 5-YR throughout the follow-up, while 7% of patients failed to achieve 1-YR ever. Thus, half of the patients eventually entered 5-YTR without relapse and a fifth after relapse. A later study on the outcome at 45 years of follow-up reported that 66% of 133 patients were in 10-YTR and 50% were in 10-YTR without ASM over the preceding five years [15]. 10-YR did not guarantee lasting seizure freedom because seizure relapse occurred in 29% of patients

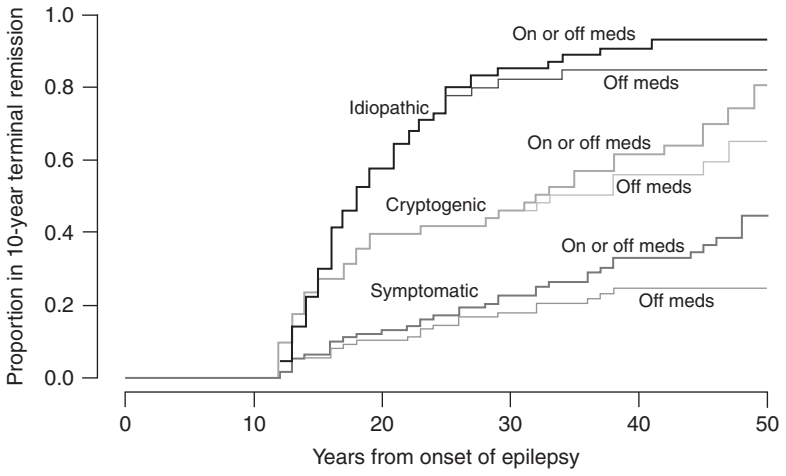

Figure 1.2 10-year terminal remission rate in relation to aetiology of seizures in 50 years of follow-up of the Finnish Childhood Onset Epilepsy(TACOE) cohort (with permission from [15])

Thick lines indicate 10-YTR on anti-seizure medications and thin lines indicate 10-YTR off medications during the last five years of follow-up.

All 245 cases in the cohort, including those who subsequently died, were lost or withdrew, are included to the analysis.

who had achieved at least one 10-YR. The outcome was strongly influenced by aetiology. Most idiopathic cases attained resolved epilepsy state (10-YR without ASM for at least five years) and did so within 30 years. Cryptogenic cases took longer to do so, and achieved remission by 45 to 50 years to an extent that approached that of idiopathic cases. The remission rate in symptomatic cases remained relatively low even after 45 years, but its slope was still up-going (Figure 1.2).

A Connecticut paediatric cohort consisted of a prospective community-based registry of children with newly diagnosed epilepsy [16]. Among 516 patients who had follow-up for at least 10 years, 95% experienced 1-YR and 257 (52%) relapsed after the initial remission with more than half regaining remission. Complete remission (CR: seizure-free and ASM-free for at least five years) was achieved by 328 (63.6%), but 23 of these patients (7%) had subsequent relapses. In summary, 60% of patients achieved CR, while 5% failed to achieve any 1-YR during the course; 35% of patients were between CR and medication-resistant epilepsy (MRE) with chronic epilepsy that had not resolved.

A Dutch hospital-based paediatric cohort study included children aged 1 month to 16 years with newly diagnosed epilepsy [17]. Among 413 patients who were followed-up for 15 years, 293 (71%) of patients had 5-YTR and 62% were receiving ASMs. Epilepsy was still active (one or more seizures during the past five years) in 120 (29%) subjects and 35 (8.5%) subjects were intractable in the final year of follow-up. Comparison of seizure outcome at 2, 5 and 15 years suggested that 48.4% had a favourable course (no seizures throughout) and 29% had an improving course with seizures in the second year, but with remission in the fifth year or later. Clinical courses in remaining patients were categorized into poor course (9.9%), deteriorating course (6.1%) and varying course (6.5%).

These paediatric cohorts provided relatively comparable long-term courses consisting of about 67% of the study population achieving prolonged remission and 50–60% of patients discontinuing ASMs. Another 33% of patients showed dynamic courses characterized by alternating periods of 'remission and relapse' and a minority (5–10%) did not achieve any 1-YR (Table 1.1). However, individual patients have unique paths, and this is not easily summarized by the remission status at the end of an arbitrary follow-up period.

Natural History of Medication-Resistant Epilepsy

The long-term outcome of newly diagnosed epilepsy is generally expected to be favourable for most patients; however, a substantial minority continue to experience seizures in spite of a range of ASMs at typically therapeutic doses in either monotherapy or polytherapy. Those patients with MRE are characterized by higher mortality and morbidity, risk of medication adverse effects, higher stigma and social handicap, higher somatic and emotional comorbidities, and compromised quality of life. The natural course of patients with MRE is an essential research area to establish effective strategies for the relief of epilepsy burden.

Table 1.1 Patients with clinical courses of newly diagnosed epilepsy in selected studies

Studies	Number of patients	Duration of follow-up (years)	Clinical courses					Relapse
			Terminal Remission			Remission		
			Early	Late	Total	Ever	None	
Anneqers et al., 1979 [7] – Population based – Children and adults	457	20	–	–	70%	76%	24%	16%
Brodie et al., 2012 [13][a] – Hospital Based – Adults	1098	7.5	37%	22%	58%	–	25%	15%
Bell et al., 2016 [9] – Population based – Children and adults	354	23.6	27%	22%	82%	–	8%	42%
Sillanpää and Schmidt, 2006 [15] – Population based – Children	144	37	16%	32%	67%	81%	27% (7%[b])	27%
Berg and Rychlik, 2015 [16] – Population based – Children	516	17	33%	10%	72%	81%	5% [b]	16% (52%)[c]

Remission indicates five-year remission except Brodie et al. [13]

[a] Remission indicates longer than one-year terminal remission.

[b] Proportion of patients who failed to achieve one-year remission.

[c] Proportion of patients who did relapse after achievement of one year or more remission.

Definition

The conceptual definition of medication resistance is 'failure to control seizures despite trials of all available ASMs in both monotherapy and combination therapy', but this is not applicable in clinical practice because of the interval of time needed to determine response to treatment and the multiplicity of ASM combinations. The historical lack of consensus on the practical definition of MRE has generated significant confusion in research and communication. Berg et al. applied several previously published definitions to their own paediatric cohort to compare the sensitivities and predictive values of individual definitions [18]. The proportion of subjects meeting the criteria for individual definitions in the cohort varied from 9% to 24%, with considerable differences in predictive values for later outcome, which raised concerns about the lack of consensus on the definition of MRE. In 2010, an ILAE Task Force proposed an operating definition of MRE, which defined drug resistant-epilepsy (DRE) as the failure of adequate trials of two tolerated, appropriately chosen and used ASM schedules to achieve sustained seizure freedom for either longer than one year or at least three times the longest inter-seizure interval, whichever is longer [19]. Use of the failure of the first two ASM treatments as the criterion was based on the observation that if two appropriate ASMs have failed to produce seizure freedom, the probability of success with subsequent ASM treatments is low [13]. The Task Force also recognized that the classification of a patient's epilepsy as medication resistant at a given point in time is valid only at the time of the assessment and does not necessarily imply that the patient will never become seizure-free on further manipulation of ASM therapy. Therefore, the ILAE definition is considered not to be the final confirmative diagnosis of medical 'intractability', but rather 'resistance', and a useful guideline for practicing neurologists in referring patients to dedicated epilepsy centres. The ILAE definition is discussed in detail in Chapter 3.

Epidemiology

Picot et al. conducted an epidemiological study in a medium-sized city in France to find 360 patients older than the age of 15 years with active epilepsy [20]. The age-adjusted prevalence rate was 5.4 per 1000 and the percentage with uncontrolled epilepsy (one or

more seizure/year) was 22.5%, corresponding to a prevalence of 1.36 per 1000. Among those with uncontrolled epilepsy, 57.1% had tried two first-line drugs, 23.8% had tried three and 16.7% had tried four or more treatments. The seizure frequencies varied across these patients, with 32% having more than one a week, 43% having between one a week and one a month and 25% having fewer than one a month. Thus, patients with one or more seizures a month constituted 15.6% of patients with active epilepsy, corresponding to a prevalence of 0.84 per 1000. Among patients with MRE, localization-related epilepsy comprised 75.3%, idiopathic generalized epilepsy 6.2% and cryptogenic or symptomatic generalized epilepsy 6.2%.

A Connecticut paediatric cohort study showed that 14% of 603 patients met the stringent criteria of intractability (one or more seizures per month for 18 months) and 23% met the criteria of two ASM failures, which was in agreement with the French adult-prevalence study [20,21]. In the Dutch paediatric cohort, at least 12% of patients had a period of intractability (not seizure-free for longer than 3 months during the previous 12 months) during a 15-year follow-up, and 8.5% were intractable in the final year, suggesting a gradual reduction of patients with MRE over long-term follow-up [22]. In a hospital-based cohort of adults with newly diagnosed epilepsy, 35.4% of 780 patients did not achieve 1-YTR and an additional 42 (5.4%) patients failed to achieve 1-YTR after relapse following initial remission at a follow-up of 79 months [12]. Thus, about 40% of patients were considered to have MRE, which was somewhat higher than paediatric cohorts.

Timing of MRE Diagnosis

The assumption that MRE will be apparent at the time of epilepsy onset has not been fully supported by either retrospective or prospective studies [10,12]. A large US multi-centre study found that the average time from onset of epilepsy to the diagnosis of MRE was 9.1 years [23]; 26% of patients with MRE had a history of 1-YR remission at some point during the course of their disorder and a prior 5-YR remission was reported by 8.5% of study participants. Onset before the age of five years was strongly associated with longer latency time to the diagnosis of MRE and higher probability of past remission. In the Connecticut paediatric cohort study, temporal patterns of MRE were dependent on the epilepsy context; when accompanied by developmental delay, 52% of 67 children met the criteria of MRE, but only 14% of children showed delayed diagnosis of MRE [21]. Among 203 children with genetic epilepsy syndromes without developmental delay, only 8 (4%) were diagnosed as MRE and 3 of them had a delayed MRE diagnosis. Of 294 children with focal epilepsy, 39 (13%) were diagnosed with MRE during the follow-up periods and 18 (46%) had a delayed appearance of MRE, with 13 having at least 1-YR before the diagnosis of MRE (Figure 1.3). Among focal epilepsies, temporal lobe epilepsy (TLE) had the highest probability of MRE (24%), as compared to other lobar epilepsies (11%)

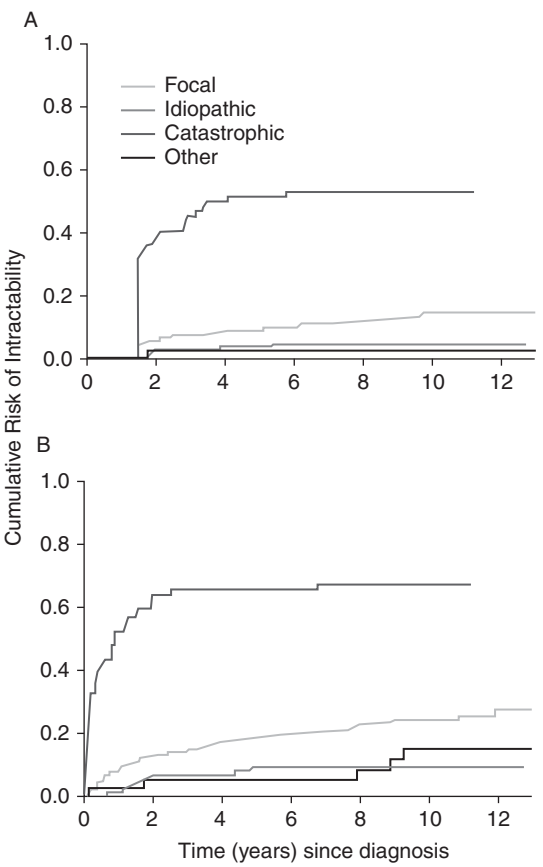

Figure 1.3 Cumulative risk for development of intractable epilepsy by syndrome groups(with permission from [21])

Red lines indicate focal epilepsy; green lines for idiopathic epilepsy; blue lines for catastrophic epilepsies; and black lines for others. (A) The stringent criteria for intractable epilepsy: ≥1 seizure/month for 18 months after the failure of two anti-seizure medications. (B) The criteria for the ILAE practical definition: failure of two anti-seizure medications and not seizure-free for one year or three times the longest inter-seizure interval, whichever is greater.

or unlocalized epilepsies (7%); however, the temporal patterns of developing MRE did not differ significantly.

In the Dutch paediatric cohort, 15 (3.3%) of 453 patients were medication resistant only during the first five years, 19 (4.2%) were medication resistant during both the first five years and the last year (15th year) of follow-up, and 16 (3.5%) had a late onset (more than five years after onset) of medication resistance, sometimes after long periods of remission [22]. Therefore, many patients had a changing MRE diagnosis during their illness, which indicates a highly dynamic epilepsy course. No significant predictive characteristics were found across these three groups.

The dynamic course of MREs was also reported in adult hospital-based cohorts. Schiller reported that 40% of 256 patients who achieved remission for one year or more had a seizure relapse at five years after entering remission, with 16% of them ultimately developing MRE [24]. In another study, a hospital cohort of 290 patients with MRE, Neligan et al. found that 70% of patients had a continuous pattern of seizures (no remissions after the onset of epilepsy) and the remaining 30% had an intermittent pattern [25].

These observations imply that the presentation of MRE is not straightforward and early identification of MRE may be elusive in a significant proportion of patients.

Predictive Factors for MRE

Identification of patients with MRE at an early stage of treatment is important in determining whether to consider alternative therapies, referral to epilepsy centres, parental counselling and individual support. Previous studies have proposed a long list of predictive factors for future development of MRE, which are divided into epilepsy-related, patient-related and treatment-related (Table 1.2) [21,26,27]. Many variables are directly or indirectly inter-related. For example, a symptomatic aetiology may include MRI lesions, focal neurological deficits and cognitive deficits. Younger age of onset may also relate to symptomatic or cryptogenic generalized epilepsies, which are common during infancy and early childhood. As such, caution is recommended when considering proposed predictive factors from different studies.

Among the long list of predictors of MRE, 'aetiology and epilepsy syndromes' was the most consistent factor, followed by high numbers of seizures or seizure density prior to initial treatment. The presence of an MRI lesion has been proposed as an important predictor; however, hippocampal sclerosis, cortical malformation and traumatic brain lesions were specific MRI lesions predicting worse outcome while other lesions were not predictive in a large-scale hospital-based study [28]. Most other predictors were either inconsistent or conflicting across studies. Even among patients with a symptomatic aetiology of epilepsy, up to 60% of children were able to enter long-term remission with prolonged treatment, which indicates a lack of any reliable way to identify medication resistance at presentation [29].

Other investigators proposed failure of the first ASM as a reliable predictor for MRE [10,12,34]. Kwan and Brodie reported that patients whose first ASM failed due to inefficacy have only an 11% chance of seizure freedom in subsequent ASM trials [10]. Dlugos et al. reported that failure of first ASM was the only variable predicting MRE in children with TLE, which was associated with high positive and negative predictive values [34]. However, Camfield et al. reported a case series of 72 children whose first ASM failed and found that 42% of them later achieved seizure freedom and only 29% had MRE at the end of eight years of follow-up [35]. A follow-up analysis of

Table 1.2 Predictive factors for MRE proposed from previous investigations

Disease-related factors	Symptomatic aetiology, including MRI lesions, partial seizures, multiple types of seizure, symptomatic generalized epilepsy High seizure frequency before treatment High seizure density before or during early treatment, seizure clustering during drug treatment Duration of epilepsy Electroencephalogram (EEG) abnormality Status epilepticus
Patient-related factors	Neurological deficits, mental retardation, developmental delay Early childhood age of onset Psychiatric comorbidities Non-adherence to ASMs, poor lifestyle, use of alcohol and recreational drugs Family history of epilepsy History of febrile convulsion or neonatal seizures
Treatment-related factors	Early response to drug treatment Delayed time to remission after treatment start

From: [6,12,21,22,26–33]

the SANAD trial found that 70% of patients whose first ASM failed later achieved 1-YR at five-year follow-up, which occurred in 65% of patients whose ASM failed due to inefficacy and 80% of those whose ASM failed due to adverse effects [36]. Therefore, the significance of failure of first ASM seems to be more reliable for childhood TLE and requires a further confirmation by other studies.

Trajectory of Medication-Resistant Epilepsy

The long-term outcomes of patients with MRE were considered pessimistic; however, several follow-up studies from tertiary epilepsy centres have reported that 20% to 30% of patients with highly refractory epilepsy have achieved late, prolonged remission with long-term follow-up. Luciano and Shorvon reported that systematic add-on ASM trials in 155 patients with chronic and highly refractory epilepsy resulted in 1-YR in 28% of patients [37]. Callaghan et al. and Choi et al. reported remission rates of 4–5% per year in their cohorts of refractory patients [38,39]. About two-thirds of them relapsed again after remission, but often with significant improvement in seizure frequency. This is a more optimistic outlook for MRE than previously believed and has kindled research interest in the long-term trajectory of patients who satisfy the ILAE criteria for MRE.

Berg et al. reported a long-term outcome (median 10.1 years) for 128 patients for whom two first-line ASMs had failed [40]; 57% of them achieved 1-YR, but 68% of these had relapses. At the last clinic visit, 1-YTR and 3-YTR were achieved in 38% and 23%, respectively. In multi-variate analysis, 'symptomatic aetiology' was the only negative predictor for 3-YTR. Among 69 patients with idiopathic or cryptogenic aetiologies, 22 (32%) patients achieved 3-YTR, while only 6 (10%) of 59 patients with symptomatic epilepsy did so. Wirrell et al. reported the long-term outcome of 75 patients who met the ILAE criteria of MRE during the first two years of treatment [41]. At follow-up of 11.5 years, 45% of them remained medically intractable, but another 45% were seizure-free on and off ASMs. Neuroimaging was the single most important predictor, with only 9% of patients with abnormal neuroimaging achieving seizure remission, compared to 60% of patients with normal neuroimaging. Both paediatric cohort studies strongly indicated that patients with ILAE-criteria MRE still have a good chance of achieving prolonged remission when the epilepsy is idiopathic or cryptogenic.

Recently, Choi et al. reported the trajectory of adult patients starting a third ASM after failure of two ASMs at a tertiary medical centre. Over the mean follow-up period of 65 months, 212 (53%) of 403 patients did not achieve a 1-YR, 63 (16%) had a complex trajectory of 'remission and relapse', 62 (15%) achieved seizure freedom after one year of treatment (delayed TR) and 66 (16%) had an early TR (within one year of treatment) [42]. Independent predictors associated with more favourable outcomes were epilepsy type and length of follow-up. TLE and generalized epilepsy were predictors of poor outcome. Remission rate was higher in patients with cryptogenic epilepsy than in symptomatic aetiology (37% vs. 25%), but the difference was not significant. The longer the follow-up, the more likely the patients were to experience a better trajectory, which was in agreement with the outcome of lifelong follow-up of patients with chronic MRE showing increasing rates of spontaneous remission in patients surviving to older age [43].

Mortality

PWE have increased premature mortality compared to the general population: almost twice as high in cryptogenic epilepsy, three to four times in symptomatic epilepsy, but not elevated in idiopathic epilepsy [44]. Mortality is highest in childhood epilepsies due to congenital or developmental causes (Table 1.3). The highest standard mortality ratio (SMR: the ratio of the observed deaths in the study population to the expected deaths in the population from which it came) is found in children, primarily due to the low mortality in the reference population and the high mortality in children with epilepsy and neurological deficits. However, the highest excess mortality was found in the elderly, which was 47/1000 person-years, or eight times higher than mortality in children with epilepsy (6/1000 person-years) [45].

The increase in mortality is most pronounced during the first years following diagnosis. In an NGPSE study, the SMR was 6.5 in the first year, decreased to 2.4 in the second year, stayed between 1 and 2 during years 5–10, and then gradually increased to >2 up to 25 years (Figure 1.4) [46]. A similar temporal pattern was also found in other population-based cohorts [45]. The reasons for a continuously high SMR persisting throughout the illness or a late increase of SMR in these cohorts are not clear, although adverse effects of chronic ASM treatment, increasing incidence of comorbidities among patients

Table 1.3 Pooled relative excess mortality risk in epilepsy by clinical characteristics across all age groups, including population-based and representative hospital-based cohorts (modified from [44])

	Incidence cases		All cases (including prevalent)	
	Pooled RR	95% CI	Pooled RR	95%CI
Aetiology				
Idiopathic/cryptogenic	1.56	1.36–1.79	1.61	1.42–1.82
Idiopathic	1.29	0.75–2.20	1.05	0.55–2.01
Cryptogenic	1.75	1.20–2.54	1.75	1.20–2.54
Symptomatic	4.73	3.27–6.83	4.48	3.24–6.21
Congenital or developmental causes	10.27	4.03–26.17	10.27	4.03–26.17
Seizures				
Seizure-free or five-year terminal remission	0.97	0.73–1.30	1.56	1.14–2.13
Highest seizure frequency category	4.69	1.41–15.60	4.65	2.70–8.01

Abbreviations: CI = confidence interval; pooled RR = pooled relative risk of death in epilepsy in a random-effects model.

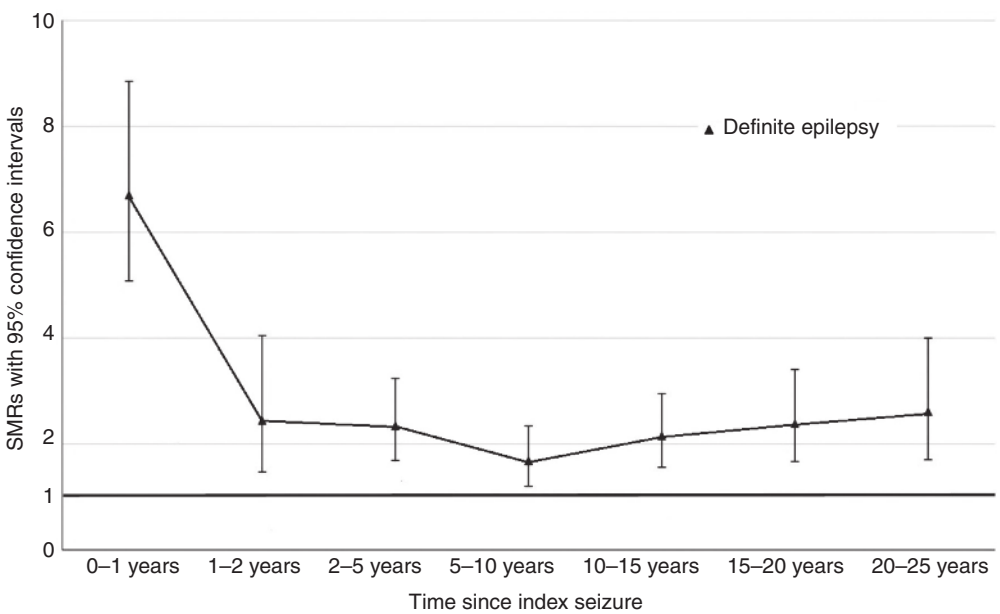

Figure 1.4 Mortality by years of follow-up from index seizure in people with definite epilepsy in UK-NGPSE study (modified with permission from [46]). Mortality is highest during the first year and rapidly decreases to an SMR level between 1 and 2 at 5–10 years after index seizure. Thereafter, SMR gradually increases and remains above 2.0 at 25 years of follow-up.

with chronic epilepsy and potential genetic influences have been proposed as potential explanations.

Cause of Death

Causes of death (COD) in PWE, which are classified into seizure-related and aetiology-related, are diverse, with significant differences among individual studies (Table 1.4).

Proportionate mortality ratio (PMR; ratio of the number of deaths for a particular cause in a study population to the total number of deaths in the same period) in population-based studies was 12–17% for cerebrovascular diseases, 12–37% for ischaemic heart diseases, 18–40% for neoplasia (including brain tumours), 8–18% for pneumonia, 0–7% for suicides, 0–12% for accidents, 0–4% for SUDEP, 0–10% for

seizure-related causes (including status epilepticus) and 5–30% for other causes [47]. Seizure-related causes play a minor role in increased mortality in population-based incident studies, whereas they are found more frequently in studies of prevalent cases having chronic epilepsies. In particular, the incidence of SUDEP is 0–0.35/1000 patient-years in population-based cohorts, whereas it increases to 1–5/1000 patient-years in epilepsy clinic populations, and to 6–10/1000 patient-years in patients who are considering epilepsy surgery [47]. In a recent NGPSE study [48], the three most common underlying causes of deaths were non-cerebral neoplasm, and cardiovascular and cerebrovascular disease, accounting for 59% of deaths, while external causes (e.g. suicide, accidents) and seizure-related causes (e.g. SUDEP) accounted for 4.2% and 3% of deaths, respectively [48]. Underlying COD was directly related to epilepsy aetiology in 23%, which was significantly more likely if death occurred within two years of the index seizure. At follow-up of 15 years and more, death in patients with idiopathic/cryptogenic cases becomes a major proportion with minor contributions from epilepsy aetiology and seizure-related causes (Figure 1.5).

Pneumonia was the most common immediate COD, accounting for 31%, followed by cancer-related conditions. Most of the patients who died had a significant number of comorbid conditions, among which neoplasm, neurologic diseases and substance abuse were independently associated with increased mortality risk. The substantial contribution of psychiatric comorbidities was also found in a Swedish national patient registry by Fazel et al., who found that external causes (suicide, accidents

Table 1.4 Classification of causes of death in patients with epilepsy

Seizure-related causes	SUDEP (definite, probable, possible) Status epilepticus Complication of seizures: includes any deaths that resulted from documented complications of a seizure (e.g. aspiration pneumonia due to seizure) or iatrogenic complications as the result of treating seizures
Natural causes	Directly related to epilepsy aetiology: death attributable to any acute or chronic neurological conditions responsible for the development of epilepsy Not related to epilepsy aetiology: death attributable to any acute or chronic medical or neurological conditions not responsible for the development of epilepsy
Non-natural causes (external causes)	Suicide Accidents: Vehicle Non-vehicle: falls, burns, drowning, drug poisoning, or other unspecified Assault
Unknown	Inadequate information available to make an attribution of the specific cause of death or to group it into the scheme above

Modified from [48–50,52]

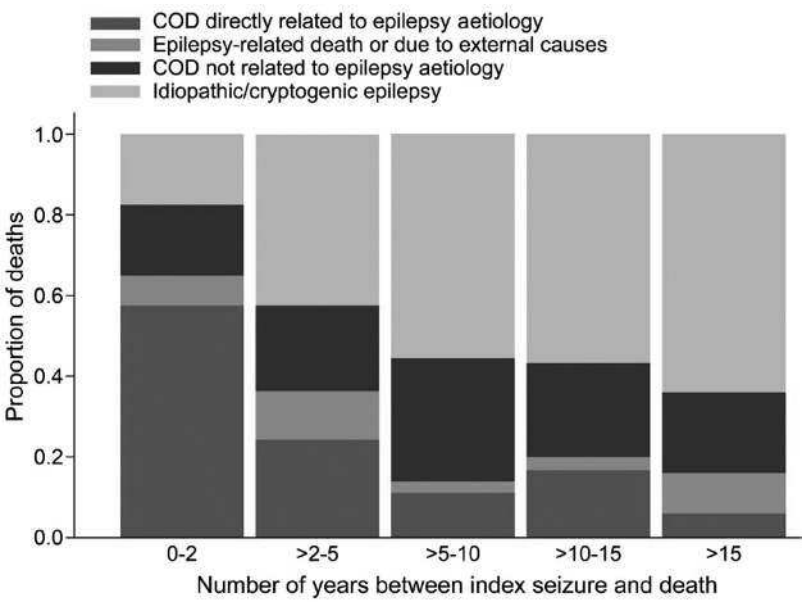

Figure 1.5 Relationship between epilepsy aetiology and underlying cause of death (COD) (with permission from [49]). During the first two years after diagnosis, epilepsy aetiology is the major COD, which declines to a minority on long-term follow-up. Mortality among patients with non-symptomatic epilepsy gradually increases to comprise more than 50% of death after five years of follow-up. Epilepsy-related deaths and external causes comprise a small proportion of mortality throughout the follow-up but their contribution increases after 15 years of follow-up.

and assaults) accounted for 15.8% of mortality in PWE, with 75% of them carrying a lifetime psychiatric diagnosis, especially a history of substance misuse and depression [49].

The Finnish paediatric cohort had the longest follow-up to provide details of premature mortality in childhood-onset epilepsy [51]. Among 245 patients, 60 (24%) died during 40 years of follow-up, which was 6.9/1000 person-years. Mortality was much higher in the remote symptomatic group and 85% of patients who died were not in 5-YR at the time of death. Death during childhood primarily occurred in the remote symptomatic group and was mostly related to the underlying disease, whereas deaths due to seizure-related causes occurred later, primarily in adolescence and adulthood. Of 60 deaths, 33 (55%) were seizure-related, including SUDEP in 18 subjects (30%), definite or probable seizures in 9 (15%) and accidental drowning in 6 (10%). The cumulative risk of SUDEP was 7% at 40 years overall and the median age of death was 25 years with the 'absence of 5-YTR' being a significant risk factor. However, the mortality outcome of the Finnish cohort was not confirmed by other subsequent studies. In a pooled analysis of four large paediatric cohorts, which included 2239 subjects with follow-up of more than 30 000 person-years, 69 died, with an overall death rate of 228/100 000 person-years [52]. Mortality rate was high only in complicated epilepsy, not in uncomplicated (idiopathic/cryptogenic) epilepsy. Seizure-related death occurred in 13 subjects (10 SUDEP and 3 others), accounting for 19% of all deaths. The SUDEP rate was similar to that for sudden infant death rates in the general population. Different outcomes between paediatric cohorts may be related to the exclusion of lethal metabolic conditions in the combined cohort study, as well as a higher proportion of remote symptomatic patients, combined incident and prevalent cases, and a longer follow-up period in the Finnish cohort [53]. In summary, COD linked to epilepsy aetiology is the major player in the earlier phase of premature mortality, whereas comorbidities unrelated to epilepsy aetiology provide a major contribution during the later phase. Seizure-related COD plays a relatively minor role throughout the course, although its contribution slowly increases during the later phase. It is likely that seizure-related COD, especially SUDEP, is more important in patients with chronic MRE.

Mortality in patients with MRE

Mortality in patients with MRE is that of prevalent cases, which is different from that of newly diagnosed epilepsy (incident cases). Premature mortality in incident cases is highest during the first two years of diagnosis, largely related to death from the underlying aetiology of epilepsy. Because the high mortality rate during the initial two years rapidly declines to a level near to that of the general population, the mortality of prevalent cases is generally expected to be lower than that of incident cases. However, in a hospital-based cohort of 2689 patients who did not respond to ASM treatment, 316 patients died during a follow-up period of 108 months, giving a crude death rate of 11.8% and an SMR of 2.04 [53]. There were 55 cases of probable SUDEP, resulting in an incidence of 2.46/1000 person-years, which was higher than the newly diagnosed epilepsy cohort (1.08/1000 person-years). Nevalainen et al. reported comparable outcomes from a hospital-based study of 1383 PWE, in which the hazard ratio of premature death was 2.66 [54]. Mortality was a product of interactions of aetiology and seizure frequencies; the SMR was 2.9 in patients with symptomatic epilepsy and seizure-free, whereas those with more than one seizure per month had a 6.3-fold higher mortality.

Callaghan et al. [55] identified 433 prevalent patients with MRE defined as failure of more than two ASMs and one or more seizures a month. Median duration of illness was 25 years and median age at the index date was 40 years. More than 80% of the population had focal epilepsy and 50% had symptomatic epilepsy; 33 patients died during the follow-up period of six years giving a case fatality of 7.6%. COD included seizure-related in 10 patients (SUDEP in 5, status epilepticus in 3, 1 accident and 1 suicide), underlying aetiology of epilepsy in 7 patients and causes unrelated to epilepsy aetiology in 16. Therefore, the contribution of seizure-related death to the increased mortality in patients with MRE was only modest, but largely related to diverse causes or comorbidities unrelated to epilepsy aetiology. However, there is accumulating evidence indicating the importance of seizure control for its preventive effects on mortality. In the study of patients with chronic MRE, SUDEP was responsible for 18% of death and high seizure frequency was a significant independent predictor of premature death, as well as SUDEP [43]. The reduction in years of life for those who had more than four