LONG-TERM PROGNOSIS OF EPILEPSY, PROGNOSTIC PATTERNS AND DRUG RESISTANCE.

A Population-Based Study

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Abstract

Aims of this study were to elucidate the long-term outcome of people with epilepsy and identify prognostic markers, including failure to achieve seizure control despite the use of 2+ antiepileptic drugs (drug resistance). Between January 2000 and December 2008 we identified from primary care records people with a diagnosis of epilepsy. Each was registered with one of 123 general practitioners in an area of Northern Italy. For each eligible case, data were collected on demographics, seizure type(s), disease duration, epilepsy syndrome, number and type of drugs (with schedules). We determined remission (uninterrupted seizure freedom lasting 2+ years) and prognostic patterns: early remission (within two years from treatment start), late remission (started after 2+ years), remission followed by relapse, no remission. Sustained remission was remission for 2+ years at any time after diagnosis and continuing until last follow-up. Terminal remission was remission for 2+ years at last follow-up.

747 individuals (381 men), aged 11 months to 94 years, were followed for 11,045.5 person-years. At the end of the study period, 428 (59%) were seizure-free. The probability of starting 2-year remission was 18% at treatment start, 34% at two years, 45% at five, 52% at ten and 67% at 20 years (sustained remission at 20 years, 60%). Epilepsy syndrome and drug resistance were the only independent predictors of 2- and 5-year remission. Early remission was seen in 101 people (19%), late remission in 175 (33%), remission followed by relapse in 85 (16%), and no remission in 166 (32%). Treatment response was the only variable associated with differing prognostic patterns.

In conclusion, the long-term prognosis of epilepsy is mostly favourable. Early remission is not invariably followed by terminal remission and outcome varies according to well-defined patterns. Epilepsy syndrome and response to two drugs predict prolonged remission while treatment response also predicts prognostic patterns.

Key-words: Epilepsy, Prognosis, Prognostic patterns, Drug resistance.

Introduction

Epilepsy is a condition with a high potential for remission. Studies in well-defined populations with newly diagnosed epilepsy have consistently shown a 1-year remission in up to 95% of people (Annegers et al., 1979; Sillanpaa and Schmidt, 2006; Berg and Rychlik, 2015; Lindsten et al., 2001; Camfield and Camfield, 2010; Camfield and Camfield 2013; Nicoletti et al., 2009; Wakamoto et al., 2000) and up to 71% are in remission at last observation with or without drugs (Annegers et al., 1979; Sillanpaa and Schmidt, 2006; Berg and Rychlik, 2015; Wakamoto et al., 2000; Goodridge and Shorvon, 1983; Geerts et al., 2010). Few studies have investigated the timing and outcome of prolonged periods of seizure freedom ("prognostic patterns") (Sillanpaa and Schmidt, 2006; Berg and Rychlik, 2015; Goodridge and Shorvon, 1983; Geerts et al., 2010; Shorvon and Sander, 1986; Neligan et al., 2011; Brodie et al., 2012). These studies have shown that early remission predicts favourable long-term outcomes. Some who fail to achieve early remission can, however, still enter remission during the course of the condition; some who experience early remission may relapse and eventually fail to achieve further remission while others may again become seizure-free. Factors such as the presence of a neurological disability (Berg and Rychlik, 2015; Wakamoto et al., 2000; Cockerell et al., 1997), aetiology (Annegers et al., 1979; Sillanpaa and Schmidt, 2006; Nicoletti et al., 2009; Geerts et al., 2010), seizure type (Annegers et al., 1979; Nicoletti et al., 2009), high seizure frequency before treatment (Wakamoto et al., 2000) and during the first months after treatment start (Geerts et al., 2010; MacDonald et al., 2000), age at diagnosis (Annegers et al., 1979), disease duration (McDonald et al., 2000), number of antiepileptic drugs (AEDs) used (Wakamoto et al., 2000), and selected epilepsy syndromes (Berg and Rychlik, 2015; Wakamoto et al., 2000) are related to the chance of remission. Age *per se* does not seem to impact the prognosis of epilepsy, but epilepsy syndromes thought to have differing prognostic significance vary between children and adults (Berg et al., 2010).

This complex picture is the background against which the recent definition of drug resistance advanced by the International League Against Epilepsy (ILAE) (Kwan et al., 2010) must be assessed. According to this definition, an individual is classified as drug-resistant when at least two correctly indicated and appropriately used AEDs fail to achieve seizure control. Using this definition, we investigated the long-term outcome in a cohort of people with epilepsy from a well-defined population, with special emphasis on pre-defined prognostic patterns. The purposes were: 1. To assess seizure outcome (and prognostic patterns) in a community-based cohort of people with epilepsy; 2. To identify prognostic indicators among selected demographic and clinical factors; 3. To define the outcome of epilepsy and the prognostic patterns of people with drug-resistant epilepsy (ILAE definition) compared with the rest of the cohort.

Material and Methods

The study population (146,506 in 2008) resided in a well-defined geographic area, the province of Lecco, Northern Italy. People of all ages with a diagnosis of epilepsy (ie. two or more unprovoked seizures at least 24 hours apart, with confirmation by a neurologist) (Commission on Epidemiology and Prognosis, 1993) who were resident in the area for at least one year between January 1st 2000 and December 31st 2008 were included and assessed retrospectively. Within this cohort comprising people with the diagnosis of epilepsy at the start of the study (prevalent cases) and those diagnosed during the study period (incident cases), a subgroup was identified who met at any time during follow-up the ILAE definition of drug-resistant epilepsy. Of the 262 general practitioners (GPs) active in the area, 123 (47%) participated in the study. Apart from age, the population represented by the study participants was similar to the population represented by the GPs who declined participation (Supplemental data, Table e-1). All medical records of people with epilepsy available in the GPs' offices and in other in- and out-patient facilities of the province (hospitals, nursing homes, ambulatory clinics) were reviewed.

In addition, to facilitate inclusion of all those with epilepsy, all participating GPs received a list of people under their care with a presumed diagnosis of epilepsy based on information contained in the claims database of the provincial health care services. This list was generated applying a validated algorithm that included requests for EEGs and the prescriptions of antiepileptic drugs (Franchi et al., 2013).

All data were collected anonymously and filed in a central database by two investigators (GG and VC) who interacted with the GPs and, if needed, with the consulting neurologists (including those outside the study area but caring for some of the enlisted individuals) for diagnostic confirmation and collection of data needed to identify epilepsy syndrome and drug response. Data were collected until death or December 31 2008 whichever came first.

For each eligible case, the following data were collected: demographics (age, sex), predominant seizure type (Commission on Classification and Terminology, 1981), disease duration, epilepsy syndrome (Commission on Classification and Terminology, 1989), number and type of drugs (with drug schedules). As the study preceded the new classification scheme for the epilepsies (Berg et al., 2010), this was not used.

Seizure outcome and prognostic patterns were classified according to pre-selected definitions. Remission was a period of uninterrupted seizure freedom lasting 2 years or longer at any time after diagnosis. We investigated 2-year and 5-year remission periods. Sustained remission was defined as seizure remission for at least 2 years at any time after diagnosis and continuing until last follow-up. Terminal remission was defined as seizure remission for at least 2 years at last follow-up with or without previous seizure relapses. Prognostic patterns were classified as: 1. Early remission: 2-year seizure freedom starting within two years from treatment start which is sustained; 2. Late remission: 2-year remission starting more than two years after treatment start which is sustained; 3. Remission followed by relapse: early or late remission followed by relapse with/without terminal remission; 4. No remission: never entering 2-year remission during the entire follow-up.

Drug-resistant epilepsy was defined as per the ILAE definition (Kwan et al., 2010). Individuals with drug-resistant epilepsy were, thus, those in whom at least two AEDs had been discontinued for lack of efficacy or those in whom a third AED, either in combination or in substitution of the previous treatment, had been prescribed. Adequacy of treatment was verified by two experienced neurologists (EBe and GE) who reviewed all data available for each individual.

Descriptive statistics are presented as counts, medians (with range), means (with standard deviations) or proportions, as appropriate. The cumulative time-dependent probability to achieve 2-year and 5-year remission, and to achieve 2-year and 5-year terminal remission, was calculated in patients followed for at least two years and five years respectively, using Kaplan-Meier curves comparing sex, age group at diagnosis, the main syndromic categories and those with or without drug-resistant epilepsy, using the log-rank test. Independent predictors of 2-year and 5-year remission (ever and terminal) were identified using the Cox multivariable proportional hazards function. Prognostic patterns were assessed in individuals with at least five years of follow-up, comparing all demographic and clinical variables with the Chi square test (or the Fisher exact test where required). Multivariable multinomial logistic regression models were used to correlate prognostic patterns with age, sex, disease duration, epilepsy syndrome, and number of AEDs. Statistical significance was set at the 5% level ($p<0.05$). All analyses were performed with SAS (version 9.2; SAS Institute, Inc, Cary, NC, USA).

The study was approved by the Ethics Committee of the Provincial Hospital of Lecco (Register number: 2011-003428-11). Local Health Service authorization was obtained to collect anonymous data from the GPs. Where GPs needed to collect additional information from individuals, informed consent was obtained. All the data were managed according to the current Italian privacy rules.

Results

As of December 31 2008, 747 individuals (381 males) aged 11 months to 94 years were included; they had been followed for a total of 11,045.5 person-years (median, 9.5, interquartile range, IQR

4.5 - 22.5). The study population included 405 prevalent cases (on January 1 2000) and 342 incident cases (newly diagnosed between January 1 2000 and December 31 2008). The two samples differed according to age and sex but not with reference to the main syndromic categories (Supplemental data, Table e-2). Six hundred and fifty seven individuals (88.0%) were followed for at least two years, 540 (72.3%) for at least five years, 365 (49%) for at least 10 years, and 207 (27.7%) for at least 20 years from diagnosis. Details are provided in Table 1. In a large proportion (42.7%) epilepsy diagnosis was at less than 15 years old. Partial seizures were the predominant type (61.6%). Partial symptomatic epilepsies were the commonest syndromic category (35.5%), followed by partial cryptogenic epilepsies (22.4%) and idiopathic generalized epilepsies (20.6%).

As of December 31st 2008, 428 people (57%) had been seizure-free for at least 2 years, 110 of them off-treatment. Thirty-one people had died by last follow-up. The cumulative time-dependent probability of starting 2-year remission was 18% at treatment start, 33.5% at two years, 44.7% at five years, 52.4% at ten years, and 67.2% at 20 years (Fig. 1A). The corresponding probability of having started 2-year sustained remission at 20 years was 59.7% (Fig. 1B). The probability of starting 5-year remission was 14.5% at treatment start and 21.5% at two years, 29.8% at five years, 34.7% at ten years and 50.2% at 20 years (Fig. 1C). The corresponding probability of 5-year sustained remission at 20 years was 42.6% (Fig. 1D). Men had a higher probability than women of starting 2-year remission and 2-year sustained remission (Tables 2A and 2B). Apart from individuals aged 75 years or older at diagnosis, the probability of starting a 2-year remission and 2-year sustained remission increased with the age at diagnosis (Tables 2A and 2B). People with partial idiopathic epilepsy had the best prognostic outlook, followed by those with idiopathic generalized epilepsies and partial cryptogenic epilepsies (table 2A and 2B). Compared to people starting a 2-year remission after treatment with one or two AEDs, those in whom three or more AEDs had failed had a significantly lower chance of entering a 2-year remission and to be in remission at last follow-up (Table 2A and 2B). The differences were similar for the probability of attaining 5-year remission and sustained remission (see Tables C and D). Only epilepsy syndrome

and drug resistance were confirmed by multivariate analysis as independent predictors of 2-year and 5-year remission (ever and sustained) (Table 3).

Syndromes and drug-resistance (ILAE definition) were found to be significantly different between those in 2-year and 5-year terminal remission and those not. Partial and generalized idiopathic and partial cryptogenic epilepsy were highly represented in the remission group, while generalized symptomatic/cryptogenic epilepsy were most represented in those not in remission at last follow-up. Significant differences were not found for sex and age at diagnosis (data not shown).

Thirteen individuals followed for at least five years had incomplete data and were excluded from the prognostic patterns assessment. The 527 remaining were had: 1. Early remission: 101 (19%); 2. Late remission: 175 (33%); 3. Remission followed by relapse: 85 (16%); 4. No remission: 166 (31%). Table 4 shows the prognostic patterns according to clinical and demographic factors. Only epilepsy syndrome, number of drugs used and response to AEDs significant determined long-term prognostic patterns. Late remission prevailed in generalized idiopathic, partial cryptogenic and idiopathic epilepsy while in generalized symptomatic/cryptogenic epilepsy or partial symptomatic epilepsy no remission was the predominant pattern. Almost one fifth (17%) of people taking one AED ever never attained remission. The percentage increased to 34% in those exposed to two different drugs and to 62% in those exposed to three or more drugs. Of people with generalized symptomatic/cryptogenic epilepsies, 36.5% attained early or late remission. Most people who failed two or more drugs (69.6%) never entered remission while 18% experienced remission followed by relapse and 11.4% had late remission. In the multinomial logistic regression models, the response to treatment was the only variable associated with differing prognostic patterns. In people with drug-resistant epilepsy, the odds ratio (OR) of having early remission was 0.03 (95% CI 0.01 to 0.25). The corresponding OR for late remission was 0.11 (95% CI 0.05 to 0.25) and for remission followed by relapse was 0.39 (95% CI 0.19 to 0.82)($p<0.0001$).

Discussion

This is the first assessment of long-term outcome of epilepsy in the general population using at the same time prognostic patterns and the recent ILAE definition of drug-resistant epilepsy. We found that at 20 years 67% of people with epilepsy had attained a 2-year remission of seizures and 50% a 5-year remission. Of these, 60% and 43% had sustained remission. Seventeen percent of people with at least 2 years of follow-up were off treatment at last observation. This is in keeping with other long-term follow-up reports. In a prospective study of 144 people with epilepsy of childhood onset in Finland (selected from a cohort of 245 children), followed for an average of 37 year (Sillanpaa and Schmidt, 2006), 48% of people were in 5-year terminal remission (early remission, 16%; late remission, 32%). The UK National General Practice Study of Epilepsy included 729 people of all ages from 275 general practices, followed for a median of 7.1 years (Cockerell et al., 1997). Seventy-one percent entered 5-year remission and 54% were in terminal remission. Remission rates higher than ours have also been reported. In a retrospective study of people with newly diagnosed epilepsy in Rochester, Minnesota, and followed for at least 5 years (Annegers et al, 1979) 76% attained 5-year remission at 20 years and 50% were off-drugs at last follow-up. In that study, an incident cohort was identified while our data included a prevalent cohort that, by definition, may have missed people with childhood-onset epilepsy who entered remission outside the study period. Our lower probability of 2-year and 5-year remission can be also explained by the shorter period of follow-up after diagnosis. One third entered remission 20 or more years after diagnosis and 15 of them (5.4%) even after 40 years. It may be that, with longer follow-up periods, our remission rates would have increased. In an extended follow-up of a retrospective cohort of people with epilepsy seen in a UK population of 6,000 from a single general practice (the Tonbridge study), 74% of interviewed individuals had achieved 4-year remission at 10 years (Cockerell et al., 1995). That study included individuals with at least one non-febrile convulsion and this implies the inclusion of people with single unprovoked seizures, who have a lower risk of relapse (Hauser et al., 1998; Hesdorffer et al., 2009).

Seizure remission tended to increase with age at diagnosis (apart from the oldest age group). Other studies in childhood-onset epilepsy provided 5-year remission rates higher than ours (Berg and Rychlik, 2015; Wakamoto et al., 2000; Geerts et al., 2012). The role of age in predicting the long-term outcome of seizures is contradictory (Annegers et al., 1979; Hart et al., 1990) and in our study, although those with onset of seizures below age 15 years had the lowest chance of experiencing seizure remission, a trend was not confirmed, even when adjusting for epilepsy syndrome.

People with generalized symptomatic/cryptogenic epilepsies and those with partial symptomatic or cryptogenic epilepsies had lower remission rates than those with other epilepsy syndromes, in line with expectations. We found, however, that remission can also occur in these syndromic categories, as previously reported (Sillanpaa and Schmidt, 2006; Berg and Rychlik, 2015; Geerts et al., 2010). These findings support the concept that the long-term prognosis of epilepsy in people with epileptic encephalopathies is not invariably poor in population-based studies.

About one fifth of our individuals entered early remission, one third entered late remission, one sixth had remission followed by relapse, and one third never entered remission. These findings are difficult to compare with other reports as the definitions of the patterns differ. In the Tonbridge study (Cockerell et al., 1995), 49% of people with seizures only at the early stage entered terminal remission ("burst" pattern, to some extent comparable with our early and late remission), 12% had remission periods followed by relapses ("intermittent" pattern, partly overlapping our remission followed by relapse pattern) and 21% had no remission ("continuous" pattern, not dissimilar from ours who never remitted). The differences can be explained by the shorter follow-up in the Tonbridge study; some people with a "burst" pattern might later relapse and enter the "intermittent" pattern. Remission followed by relapse was observed in 6% of people in the Rochester, Minnesota cohort (Annegers et al., 1979). A more detailed distribution of prognostic patterns has been used in a study that followed 516 children with epilepsy for 10+ years and identified eight seizure remission patterns ranging from early 1-year remission, no relapse and complete remission at last follow-up (33%) to never achieving 1-year remission (5%) (Berg and Rychlik, 2015). The shorter period of

remission (1-year vs. 2-year in our study) may explain in part the higher rates of individuals with early remission and the lower rates of people never achieving remission.

The classification of an individual as drug resistant according to the ILAE definition was compatible with a thirty percent chance of early or late remission after treatment failure. These findings are in keeping with population-based studies done in children and adult cohorts followed for prolonged periods of time (Neligan et al., 2011; Brodie et al., 2012; Geerts et al., 2012; Berg et al., 2009) and confirm the concept that the failure of two AEDs is still compatible with the possibility of prolonged seizure remission later during follow-up. Our findings are in line with a recent report on a cohort of adults with chronic refractory epilepsy with long-term follow-up in an epilepsy clinic (Neligan et al., 2012).

The only variable predicting the prognostic pattern was the response to AEDs and, more specifically, drug resistance (ILAE definition). Prognostic patterns can be anticipated by the response to the first treatments rather than to the inclusion of an individual in a broad syndromic category.

Our study has strengths and limitations. A major strength is the population base with a large sample of individuals of all ages with at least five years of follow-up. This allowed us to determine seizure patterns. The first major limitation is that the study has been undertaken in a cohort with prevalent and incident cases rather than a pure incident cohort and without knowledge of the outcome in incident cases (except for those newly diagnosed during the study period). When comparing the prevalent and incident cohorts, the two groups differed according to age and sex but not to the major syndromic categories (the only variable, together with treatment response, predicting long-term remission). Another major limitation is the retrospective nature of our study, as this has several implications. First, in the absence of a predefined, standardized modality to collect the necessary information, we were unable to assess accurately treatment efficacy. As a result, the identification of people with drug-resistant epilepsy may not have been entirely accurate. Second, two investigators evaluated the course of treatment in each individual and verified whether treatment

was appropriate for the presumed diagnosis but it is possible that some of these individuals did not have epilepsy and were thus unlikely to respond to AED treatment. Future studies should address this issue in order to prevent unwarranted distortion of findings. Third, we did not apply the rule of three that completes the ILAE definition (Kwan et al., 2010) (i.e., in order for epilepsy to be drug-resistant, the seizure-free period should be less than three times the pre-intervention inter-seizure interval or less than 12 months, whichever is longer) as pre-treatment seizure frequency was not available and we were interested in assessing remission periods lasting at least 2 years. Fourth, our follow-up was limited and this may account at least partly for the differences between our findings and better outcomes reported in studies with longer duration. A final limitation is the classification only into broad syndromic categories, which prevented us from providing an outlook for people with specific diagnoses.

In summary, the long-term prognosis of epilepsy in a community-based cohort is favourable in about one-half of cases. Seizure remission is followed by discontinuation of treatment in one sixth. Early seizure remission does not, however, invariably lead to terminal remission. Our study confirms that seizure outcome varies according to specific patterns but it shows that prolonged seizure remission and prognostic patterns can be predicted only by the response to the first two AEDs. The poor response to two appropriate AEDs is, however, compatible with the possibility of entering prolonged remission and even achieving terminal remission, stressing the dynamic nature of drug-resistance, but it is a robust indicator of a poor long-term prognosis and prognostic patterns.

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Figure 1. Cumulative time-dependent probability of attaining 2-year remission (A), 2-year sustained remission (B), 5-year remission (C), and 5-year sustained remission (D) in the study cohort

Table 1. General characteristics of the sample (n=747)

Variable	Category	N	%
Gender	F	366	49.0
	M	381	51.0
Family history of seizures	Yes	111	14.9
	No	584	78.2
	Unknown	52	6.9
Seizures	Partial	460	61.6
	Generalized	260	34.8
	Unclassifiable	27	3.6
Syndrome	GC/GS	74	9.9
	GI	154	20.6
	PC	167	22.4
	PI	54	7.2
	PS	265	35.5
	Undetermined	26	0.9
	Special	7	3.5
Age at diagnosis	<15y	318	42.7
	15-34y	183	24.6
	35-54y	120	16.1
	55-74y	100	13.4
	75+y	24	3.2
	Missing	2	
Disease duration at diagnosis	<1y	666	89.5
	≥1 y	78	10.5
	Missing	3	
Number of AEDs	0	16	2.1
	1	393	52.6
	2	199	26.6
	3+	139	18.6
Drug resistant	No	640	85.7
	Yes	107	14.3

Legend: W = women; M = Men; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; GI = Generalized Idiopathic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years; AED = antiepileptic drug.

Table 2. Cumulative time dependent probability of attaining 2-year remission, 2-year sustained remission, 5-year remission, 5-year sustained remission by selected demographic and clinical variables. Univariate analysis

	A. Cumulative probability of starting a 2-year remission						B. Cumulative probability of starting a 2-year sustained remission						C. Cumulative probability of starting a 5-year remission						D. Cumulative probability of starting a 5-year sustained remission					
Years of follow-up	**0**	**2**	**5**	**10**	**20**	**p-value**	**0**	**2**	**5**	**10**	**20**	**p-value**	**0**	**2**	**5**	**10**	**20**	**p-value**	**0**	**2**	**5**	**10**	**20**	**p-value**
Sex						0.0035						0.0202						0.0020						0.0150
M	21.5	37.6	49.9	56.7	72.4		14.6	28.9	41.3	49.2	65.6		14.4	26.1	35.8	39.1	57.4		9.8	19.4	28.0	31.7	49.5	
W	14.0	28.9	39.0	47.7	62.0		10.9	23.1	32.6	40.5	54.1		9.5	16.9	23.7	30.1	43.6		7.5	14.0	20.1	25.0	36.8	
Age at diagnosis						<0.0001						<0.0001						0.0001						<0.0001
<15y	13.3	27.3	36.1	43.3	57.1		9.6	20.4	28.4	35.5	48.0		8.0	15.5	22.1	27.1	41.4		5.3	11.3	17.0	21.1	33.4	
15-34y	20.8	35.2	47.5	54.0	70.8		13.9	25.8	37.8	44.8	62.3		15.0	22.9	32.9	36.9	55.4		10.0	16.9	24.7	28.4	46.0	
35-54y	22.2	36.4	48.2	56.3	79.1		17.2	31.2	43.0	50.5	76.3		15.2	26.6	32.9	40.9	57.6		12.7	23.1	29.8	36.5	54.4	
55-74y	20.8	45.5	60.6	78.6	91.5		16.9	39.2	55.0	75.6	90.2		14.8	35.2	46.5	49.2	77.8		13.0	28.7	41.2	44.1	75.5	
75+y	27.8	44.4	62.5	62.5	-		11.8	32.1	54.2	54.2	-		16.7	25.0	41.7	41.7	-		8.3	17.5	35.8	35.8	-	
Syndrome						<0.0001						0.0001						0.0001						0.0001
GC/GS	6.5	17.7	17.7	32.9	40.9		4.8	11.6	11.6	27.9	33.7		7.7	11.5	11.5	20.3	26.2		5.8	5.8	5.8	15.1	18.2	
GI	21.1	35.3	52.3	59.8	73.9		14.3	24.5	41.3	48.5	65.5		14.2	23.0	37.2	42.5	59.1		9.7	18.2	30.7	34.3	52.1	
PC	19.9	36.9	52.2	60.8	72.8		13.6	29.2	45.5	54.4	65.6		14.2	23.3	31.7	35.8	47.3		10.0	18.0	26.1	29.3	37.7	
PI	23.9	45.7	54.4	66.2	86.4		19.6	39.1	48.8	62.1	83.1		13.9	25.0	41.7	51.2	80.4		11.2	22.7	34.6	45.4	75.6	
PS	15.2	30.9	40.3	44.4	61.6		12.0	26.2	34.7	38.5	55.3		8.3	20.1	25.4	28.2	44.2		7.1	16.3	21.9	24.0	38.9	
Special	40.0	60.0	60.0	60.0	60.0		20.0	46.7	46.7	46.7	46.7		40.0	60.0	60.0	60.0	60.0		20.0	46.7	46.7	46.7	46.7	
Undetermined	30.0	40.0	45.0	50.5	62.9		15.0	27.1	27.1	34.4	42.6		18.8	25.0	31.3	37.5	52.4		6.3	13.5	13.5	21.3	30.1	
Drug resistant						<0.0001						<0.0001						<0.0001						<0.0001
No	20.6	37.6	50.1	58.5	74.9		15.2	30.3	42.7	51.6	68.6		13.7	24.5	34.1	39.8	58.4		10.2	19.7	28.2	33.5	51.6	
Yes	3.2	10.6	14.0	17.9	24.9		0.0	3.4	5.7	8.5	12.6		2.5	5.1	6.3	7.7	11.5		0.0	0.0	1.3	1.3	1.3	

Legend: W = women; M = Men; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years.

Table 3. Selected demographic and clinical predictors of 2-year and 5-year remission. Multivariate analysis

		2-year remission						5-year remission					
		All			Sustained			All			Sustained		
Variable	**Category**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Gender				0.3160			0.7963			0.1041			0.3859
	F	ref.			ref.			ref.			ref.		
	M	1.11	0.91 - 1.36		1.03	0.82 - 1.29		1.25	0.96 - 1.63		1.14	0.85 - 1.54	
Age at diagnosis				0.6724			0.7587			0.2096			0.3169
	<15y	ref.			ref.			ref.			ref.		
	15-34y	1.20	0.93 - 1.54		1.16	0.87 - 1.55		1.39	0.99 - 1.93		1.32	0.91 - 1.93	
	35-54y	1.04	0.76 - 1.42		1.08	0.77 - 1.53		1.38	0.90 - 2.09		1.48	0.93 - 2.34	
	55-74y	1.18	0.84 - 1.65		1.22	0.85 - 1.75		1.65	1.03 - 2.64		1.64	0.98 - 2.74	
	75+y	1.08	0.57 - 2.05		0.92	0.44 - 1.92		1.35	0.53 - 3.45		1.17	0.41 - 3.35	
Syndrome				<0.0001			<0.0001			0.0002			0.0002
	GC/GS	0.33	0.20 - 0.54		0.27	0.16 - 0.47		0.27	0.14 - 0.51		0.20	0.09 - 0.43	
	GI	0.63	0.44 - 0.92		0.51	0.34 - 0.77		0.58	0.37 - 0.92		0.51	0.31 - 0.84	
	PC	0.58	0.39 - 0.85		0.50	0.33 - 0.76		0.42	0.25 - 0.69		0.35	0.20 - 0.61	
	PI	ref.			ref.			ref.			ref.		
	PS	0.45	0.31 - 0.65		0.38	0.26 - 0.58		0.38	0.24 - 0.60		0.36	0.21 - 0.59	
	Special	0.67	0.21 - 2.21		0.51	0.12 - 2.15		1.10	0.33 - 3.72		0.89	0.20 - 3.87	
	Undetermined	0.68	0.37 - 1.25		0.54	0.26 - 1.09		0.55	0.26 - 1.14		0.39	0.16 - 0.97	
Drug resistant				<0.0001			<0.0001			<0.0001			0.0002
	No	ref.			ref.			ref.			ref.		
	Yes	0.28	0.19 - 0.43		0.16	0.09 - 0.28		0.18	0.09 - 0.35		0.02	0.01 - 0.98	

Legend: HR = Hazard Ratio; 95%CI = 95% Confidence Interval; F = female; M = Male; GC/GS = Generalized Cryptogenic/Generalized Symptomatic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years.

Table 4. Prognostic patterns by selected demographic and clinical variables

		Early remission		Late remission		Remission-relapse		Remission never		
Variable	**Category**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**p-value***
Gender	F	43	16.6	89	34.4	39	15.0	88	34.0	0.3469
	M	58	21.6	86	32.1	46	17.2	78	29.1	
Seizures	Partial	61	19.2	103	32.4	48	15.1	106	33.3	0.5234
	Generalized	38	19.5	68	34.9	32	16.4	57	29.2	
	Unclassifiable	2	14.3	4	28.6	5	35.7	3	21.4	
Syndrome	GC/GS	4	7.7	15	28.8	8	15.4	25	48.1	0.0046
	GI	25	21.0	45	37.8	22	18.5	27	22.7	
	PC	27	22.1	38	31.2	20	16.4	37	30.3	
	PI	9	23.7	20	52.6	5	13.2	4	10.5	
	PS	32	18.4	52	29.9	23	13.2	67	38.5	
	Special	2	40.0	0	0.0	1	20.0	2	40.0	
	Undetermined	2	11.8	5	29.4	6	35.3	4	23.5	
Age at diagnosis	<15y	35	14.9	75	31.9	41	17.5	84	35.7	0.3039
	15-34y	26	18.4	50	35.5	26	18.4	39	27.7	
	35-54y	21	25.9	27	33.3	8	9.9	25	30.9	
	55-74y	16	28.1	20	35.1	7	12.3	14	24.5	
	75+y	3	23.1	3	23.1	3	23.1	4	30.7	
	Missing									
Disease duration at diagnosis	<1y	88	18.6	161	34.0	73	15.4	152	32.1	0.2914
	≥1 y	13	24.5	14	26.4	12	22.6	14	26.4	

Number of AED	0	0	0.0	0	0.0	1[§]	20.0	4[^]	80.0	<0.0001
	1	80	29.7	108	40.2	35	13.0	46	17.1	
	2	19	12.9	49	33.3	29	19.7	50	34.0	
	3+	2	1.9	18	17.0	20	18.9	66	62.2	
Drug resistant	No	100	22.3	166	37.0	71	15.9	111	24.8	<0.0001
	Yes	1	1.3	9	11.4	14	17.7	55	69.6	

Legend: W = women; M = Men; GC/GS = Generalized Cryptogenic/Generalized Symptomatic;
GI = Generalized Idiopathic; PC = Partial Cryptogenic; PI = Partial Idiopathic; PS = Partial Symptomatic; y = Years;
AED = antiepileptic drugs.
* Univariable chi-square; ^ 1 patient, age 15, with GI epilepsy; 2 patients, age 88 and 74, taking only diazepam at the time of the seizures; 1 patient, age 83, with brain tumor; § 1 patient, age 31, with GI epilepsy.