Late-life terminal seizure freedom in drug-resistant epilepsy: "burned-out epilepsy"

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Abstract

The course of established epilepsy in late life is not fully known. One key question is whether the resolution of an epileptic diathesis is a natural outcome in some people with long-standing epilepsy. We investigated this with a view to generating a hypothesis. We retrospectively explored whether terminal seizure-freedom occurs in older people with previous drug-resistant epilepsy at the Chalfont Centre for Epilepsy over twenty years. Of the 226 people followed for a median period of 52 years, 39 (17%) achieved late-life terminal seizure-freedom of at least two years before death, which occurred at a median age of 68 years with a median duration of 7 years. Multivariate analysis suggests that a high initial seizure frequency was a negative predictor ($p<0.0005$). Our findings indicate that the 'natural' course of long-standing epilepsy in some people is one of terminal seizure freedom. We also consider the concept of "remission" in epilepsy, its definition challenges, and the evolving terminology used to describe the state of seizure freedom. The intersection of ageing and seizure freedom is an essential avenue of future investigation, especially in light of current demographic trends. Gaining mechanistic insights into this phenomenon may help broaden our understanding of the neurobiology of epilepsy and potentially provide targets for therapeutic intervention.

Keywords: Pharmaco-resistance, prognosis, seizure outcome, ageing

1.Introduction

Epilepsy is one of the most common serious neurological disorders, with a prevalence of 0.4 - 1% in the general population (Fiest et al, 2017, Thijs 2019,). Two-thirds of people with epilepsy enter a sustained period of seizure freedom (Sander & Kwan 2004). The remaining third have 'drug-resistant epilepsy' (DRE), a phenomenon conceptualised as a failure to respond to two appropriately chosen and tolerated anti-seizure medications (ASMs) (Kwan et al., 2010). DRE remains a significant healthcare challenge); the consequences include an increased risk of premature mortality, reduced life expectancy, diminished quality of life and significant socioeconomic and healthcare burden (Jacoby et al., 1998, Sander 2003, Schmidt and Sillanpää, 2012, Allers et al., 2015, Devinsky et al. 2015, Beghi et al. 2016).

Outside of therapeutic interventions, little is known about sustained states of seizure-freedom in the context of the natural history of epilepsy because, in high-income countries, convention favours the early initiation of seizure-suppressing treatment. The natural history of some childhood epilepsy syndromes is, however, one of resolution (Berg et al., 2014; Sillanpaa & Schmidt, 2015). While genetic and developmental factors are unquestionably influential in such outcomes, the alterations at a neuronal and network level require elucidation.

Our understanding of the natural progression of epilepsy with ageing is tenuous. The current view is that there is a low chance of attaining sustained seizure-freedom in DRE. If achieved, it usually occurs early on in the context of anti-seizure treatment, with a risk of subsequent relapse (Luciano & and Shorvon, 2007; Callaghan et al., 2007; Schiller et al., 2009; Callaghan et al., 2011; Choi et al., 2011; Sillanpää & Schmidt, 2012; Berg et al., 2014; Bell et al., 2016). A few studies on spontaneous seizure-freedom with ageing exist (Cockerell et al., 1995, Anderson et al., 2011, Novy et al., 2012), but data on this phenomenon are sparse.

Epidemiological data from low to middle-income countries, where a 'treatment gap' exists due to the unavailability of ASMs and healthcare deficiencies, has offered some insight on the course of

untreated epilepsy. An Ecuadorian study identified over 1,000 people with epilepsy, of whom about a third became seizure-free (Placencia et al., 1994). An Ethiopian study identified a high incidence of epilepsy and a lower prevalence (comparable to high-income countries) as evidence of sustained seizure-freedom (Tekle-Haimanot et al., 1997). Higher mortality, however, cannot be discounted (Bell et al., 2014). Other studies have also suggested a potentially higher frequency of sustained seizure freedom than previously proposed (Watts, 1992). The scarcity of numbers, methodological deficiencies, case ascertainment bias and differing aetiologies demand caution, but some people with epilepsy do seem to enter a state of terminal seizure-freedom.

Epilepsy prognosis can be generally divided into three main categories (Duncan & Shorvon, 1986, Sander 2003, Kwan & Sander 2004, Berg et al., 2011); in group 1, the prognosis is excellent, and resolution is the rule. Entities such as childhood epilepsy with centrotemporal spikes (CECTS) and childhood absence epilepsy (CAE) fall into this group (Grosso et al., 2005, Callenbach et al., 2010). If needed, ASM is used until the epileptogenic process remits, and once this state is attained, it tends to be permanent. In group 2, seizure suppression can occur only with the continued use of ASMs; there is a high risk of recurrence with ASM withdrawal and a tendency to long-term or lifelong treatment. In group 3, the prognosis is poor, with ongoing seizures despite using ASMs, which tend to ameliorate but never abolish seizures, although there is a subgroup that may respond to a medication not previously tried or to neurosurgical treatment (Vakharia et al., 2018). Lennox-Gastaut syndrome and mesial temporal sclerosis in adults are examples (Pittau et al., 2009, Jeong Kim et al., 2015). There is overlap between and heterogeneity within each group; epilepsies in group 1 may persist, albeit in an attenuated form, requiring treatment in adulthood; JME, which is typically associated with a persistently increased risk of seizures throughout life, can remit in up to a fifth of cases (Senf et al., 2013). In addition to the three main categories, other variations in the 'natural' history of epilepsy do exist; epilepsy may resolve after a few years of activity, enabling the discontinuation of ASMs at a young age; a relapsing-remitting course occurs in others; and finally, a recrudescence of seizures may occur after many years of dormancy.

Most reports on sustained seizure freedom are from paediatric populations, but some insights of this state in adults have been inferred from ASM withdrawal studies (MRC Antiepileptic Drug Withdrawal Group, 1991). Two general findings emerge from the collected data (Wenqui Yang et al., 2020); firstly, intermittent periods of seizure freedom of up to a few years can occur in adults with epilepsy. Secondly, factors increasing recurrence risk following medication withdrawal have been identified: adolescent or adult-onset, aetiology, time since last seizure, seizure type, syndromic diagnosis, abnormal imaging, polytherapy, presence of myoclonus are all potentially influential.

The purpose of this exercise was to generate a hypothesis that terminal seizure freedom can occur in a cohort of individuals with longstanding drug-resistant epilepsy. Therefore, we assessed the natural history of drug-resistant epilepsy among the Chalfont Centre for Epilepsy residents to investigate outcomes and ascertain whether terminal seizure freedom was associated with any identifiable predictive factors.

2.Methods

2.1 Setting and data collected

The Chalfont Centre for Epilepsy, established in 1892, provides residential care for people with epilepsy, particularly those with DRE who have additional medical and social needs. (Sander et al., 1993; Von Bredow et al., 2017).

We undertook a retrospective analysis of seizure patterns in people with DRE who died at the Chalfont Centre between 1988 and 2008 (Novy et al., 2013). Only those who fulfilled the ILAE criteria for the definition of DRE were included (Kwan et al., 2010). We collected data on the demographics, age of epilepsy onset, age at death, epilepsy duration, number of ASM tried, epilepsy type, initial frequency, aetiology, presence of intellectual disability (IQ < 70), psychiatric comorbidity (mood disorders, psychosis and generalised anxiety requiring medical intervention), history of status epilepticus, prior

periods of seizure-freedom. Seizure freedom was deemed to be linked to a therapeutic intervention if it preceded seizure cessation by at least three months. All individuals who achieved terminal seizure freedom had continued on ASMs to exclude medication changes as a cause for seizure freedom.

Initial seizure frequency was categorised for each individual, reviewing the seizure charts of the first year of admission to care. Frequency was then separated in three groups, according to seizure numbers: 1) < 1 seizure/month, but ≥ 1 per year; 2) 1-4 seizures/month; 3) frequency > 4 seizures/month.

We operationally defined terminal seizure freedom as the presence of at least two years of uninterrupted seizure freedom until death (Thurman et al., 2011). Individuals were considered as either having a continuous seizure pattern or relapsing-remitting course, based on the occurrence of any previous epochs of seizure-freedom along with their history.

2.2 Statistical analysis

We used SPSS version 18 (SPSS inc). Multivariate manual stepwise regression analyses were performed with all factors presenting a p-value ≤ 0.1 in univariate analysis. Chi-square, Fisher exact, Kruskal-Wallis, Mann-Whitney, Wilcoxon signed-rank and Spearman correlation tests were used as needed in univariate analysis.

2.3 Ethical an regulatory approval

This work was registered and independently approved by the Clinical Audit and Quality Improvement Subcommittee at UCLH University College London Hospitals Trust. This waives the need for approval by an ethics committee and individual informed consent under UK legislation and NHS operating procedures.

3.Results

3.1 General characteristics and demographic data

Two hundred and twenty-six individuals were included, admitted between 1926 and 2007, with a mean duration of residence of 29 years (range, 3 months to 73 years). Demographics and clinical characteristics are summarised in tables 1 and 2. Age at epilepsy onset was unavailable for 14 people.

3.2 Clinical course of epilepsy

Thirty-five (15%) people had a relapsing-remitting course with 1 to 3 previous seizure-freedom periods and a median cumulative duration of seizure-freedom of 4 years (range 2-28 years). Thirty-nine (17%) people reached terminal seizure-freedom; fourteen (36%) of those had had a relapsing-remitting course, while 25 (64%) had not experienced a previous period of seizure-freedom. The median onset of terminal seizure-freedom was 68 years (range 33-93), and its median duration was seven years (range 2-41 years). The median seizure-freedom duration was eight years (range 2-27) in people with a relapsing-remitting course. The duration of terminal seizure-freedom periods was significantly longer than the previous cumulative epochs of seizure-freedom (Mann-Whitney U test, $p = 0.016$).

3.3 Predictors of seizure freedom

Univariate analysis identified the following as significant predictors of terminal seizure-freedom: low initial seizure frequency, no history of status epilepticus and absence of psychiatric comorbidity (table 3). The total number of ASMs tried (OR 0.40, 95% CI 0.28, 0.57) was excluded from the multivariate analysis as this was biased by different drug availability according to the period in which people lived. There was a significant correlation between the number of ASMs tried and the year of death (Spearman Rho = 0.27, $p < 0.0001$). People who died before the availability of newer ASMs in the early 1990s had the opportunity to try only a few drugs. The occurrence of previous periods of seizure-freedom was not included in the multivariate model owing to its significant correlation with age at death ($p = 0.003$). Intellectual disability was unrelated to the chances of terminal seizure-freedom (OR 0.50, 95% Confidence Interval (CI) 0.20, 1.26). Multivariate analysis indicated that seizure frequency remained a significant predictor of terminal seizure freedom. .

4.Discussion

Our findings suggest that terminal seizure freedom may occur in people with long-standing DRE. Our data aligns with a study over 25 years ago from the same centre, which found a similar rate of 2-year seizure-freedom (Cockerell et al., 1995). Similar findings have been reported elsewhere, albeit with a one-year threshold for "remission" (Callaghan et al., 2011; Choi et al., 2011).

In contrast, in a cohort with childhood-onset epilepsy, about half of people with an initial diagnosis of DRE reached a 5-year terminal seizure-freedom (Sillanpää and Schmidt, 2012). Our cohort had a high rate of intellectual disability typically associated with a less favourable long-term prognosis and consisted of a high proportion of 'severe' cases requiring institutional care. 'Terminal seizure freedom in our exercise was also defined as seizure freedom of at least two years duration until death, as opposed to freedom for the length of follow-up, which was the criterion used in the study of childhood-onset epilepsy (Sillanpää and Schmidt, 2012).

The retrospective nature of this exercise restricted our analysis to clinical parameters, owing to the variability in available EEG and imaging data. Our cohort is also highly selected and differs from people attending tertiary centres. Indeed, this selection bias is a limitation, and the applicability to the general older population will need to be tested in future studies to determine the external validity.

Our selection of an arbitrary threshold may have incorrectly estimated terminal seizure-freedom. The proportion would not have changed if we used the "rule of three" proposed by the ILAE task force (Kwan et al., 2009). Our non-interventional approach renders it unsuitable for the alternative "rule of three-to-six" paradigm (Brandon Westover et al., 2012). The proportion of people with intellectual disability was higher than in most regular outpatient clinics of tertiary centres. Our data reflected the severely affected individuals who needed residential care, as those who exhibited milder disease or sustained seizure-freedom were more likely to have been discharged. Thus, our findings may underestimate the proportion who achieve terminal seizure-freedom. Many of the individuals died

before newer ASMs, or other modalities of investigation and treatment became available, including stimulation techniques.

Two predictors of terminal seizure freedom we found were seizure frequency and older age. Seizure frequency was the single most important predictor of long-term seizure-freedom in two prospective studies (Mac Donald et al., 2000; Sillanpää and Schmidt 2009). Our findings confirm the validity of this observation, even in the setting of long-standing DRE. Conversely, a high seizure frequency is a risk factor for early death, thus precluding individuals from potentially achieving sustained seizure-freedom in late life (Novy et al., 2013). History of status epilepticus (SE) was not associated with terminal seizure freedom, a finding which would appear to be intuitive. Speculatively, neuronal networks subserving prolonged seizures may be 'hard-wired' such that they are more resistant to age-related degradation. Psychiatric comorbidity was associated with seizure persistence and not terminal seizure freedom. The mechanisms responsible for this await elucidation, but our finding further strengthens the concept of a bidirectional link between epilepsy and psychiatric health (Mula et al, 2021).

The terminology used to describe an enduring state of seizure-freedom has evolved. Historically the term 'remission' has been favoured, although its use is contentious. Operationally, it is a retrospective designation, a function of seizure freedom and time, although the latter parameter's duration has varied from two to five years. The terms 'seizure freedom' and 'remission' are often used interchangeably. This is erroneous; whilst seizure freedom is a precondition for remission, it is possible to be free of seizures and on ASMs and yet for the underlying epileptogenic diathesis to persist. 'Remission' does not imply the absence of the disease as is often construed. Recently, under the auspices of the ILAE, a consensus of expert opinion advanced a definition of 'epilepsy resolved' (Fisher et al., 2014), proposing a criterion of 10 years of seizure-freedom, with five years off anti-seizure medications. Whilst the risk of subsequent seizures following such a time interval is likely to be low, there is very little published data on 10-year seizure-free outcomes and none in the setting of terminal seizure freedom (Sillanpaa et al., 2017). We used the term 'seizure freedom' rather than 'remission'

for two reasons. Firstly, there are no biomarkers to determine the state of a person's epilepsy. Secondly, our lack of understanding of the mechanisms responsible for either 'active epilepsy' or 'remission' means that we cannot with certainty ascertain when an epileptic diathesis has regressed or resolved.

The role of ageing in epilepsy prognosis has received little attention. A preliminary report noted that most people who entered a state of sustained seizure freedom after long-standing DRE were over 60 years of age and proposed a possible causal influence of ageing on epilepsy prognosis (Cockerell et al., 1995). We found that age was the most critical predictor of terminal seizure-freedom. This result is shared with a recent post-mortem case series on a subset of our cohort (Novy et al, 2013).

It is unknown whether epilepsy in our cohort is resolved as the majority of individuals continued on ASMs. A small study on people with a median late-life remission of 10 years after long-standing DRE reported a relapse rate of 75% after ASM discontinuation (Koepp et al., 2008). This raises the possibility that advancing age may be associated with increased ASM sensitivity, a hypothesis which may account for the generally favourable prognosis of new-onset seizures in this age group following the instigation of ASM treatment (Stephen et al., 2006; Mattson et al., 1996). An alternative explanation is that the spectrum of causes of epilepsy in older people may be more amenable to treatment. The cohort of "burned out" epilepsy may consist of two subsets; those who enter an enduring state of terminal seizure-freedom independent of ASMs – "burned out" epilepsy - and others who are prone to relapses upon ASM withdrawal.

The intersection of ageing and epilepsy is a potentially important research subject, not least because of the seemingly paradoxical nature of this relationship. The highest incidence of epilepsy is in people over the age of 65 years (Sen et al, 2020). Aetiology is demonstrable in most cases, with covert microangiopathic disease likely to account for the 'imaging-negative' cohort, but little is known of the pathophysiological mechanisms of epileptogenesis in this age group. Insights from assessing the association between dementia, particularly Alzheimer' disease, and epilepsy (Pandis & Scarmeas 2012,

Palop & Mucke, 2016, Sen et al 2018, 2020) have suggested a complex interplay of various factors, including a mechanistic link between amyloid/tau accumulation and evolving cerebrovascular changes, along with either the convergence of molecular pathways involved in each disorder or a pathological denominator common to both (Imfeld et al., 2013, Noebels, 2011, AL Gheyara et al., 2014). Conversely, older people mainly respond well to ASMs, have reasonable seizure control, and appear to experience relatively fewer convulsive seizures. There is evidence of the ageing brain's increasing refractoriness to the formation of secondary epileptic foci in human and mice models (De Toledo Morrell et al. 1991; Morrell et al., 1999; Leppik et al., 2006). In a post-mortem case series, the occurrence of secondary degenerative changes was a positive predictor of terminal seizure-freedom (Novy et al, 2013). A progressive decline in the risk of epilepsy with increasing age has also been suggested in subjects with Alzheimer's disease (Amatniek et al., 2006). This study's findings would also suggest regression of an epileptic tendency in a cohort of people with advancing age.

The neurobiological mechanisms at the molecular, genetic and network level responsible for enduring seizure-freedom remain unknown. Whilst altered gene expression and reconfiguration of networks nested within the framework of neurodevelopment may account for resolution of childhood epilepsy syndromes, the extent to which these factors and mechanisms influence late-life seizure-freedom is unknown.

The understanding of epilepsy is moving from a disease of neuronal excitability to a postulated network disorder. It is conceivable that late-onset seizure-freedom may be partly due to structural and functional alterations in cortical organisation and connectivity, such as vascular damage-causing lesions that interrupt the epileptic network. The degradation of this putative network's integrity may also partly explain the relatively rare occurrence of convulsive seizures in older people. Convulsions require intact bihemispheric pathways for rapid engagement and propagation. Conversely, sudden perturbations of brain function or the accumulation of various insults over time may be sufficient to tip the balance in favour of epileptogenicity, accounting for the increased incidence and not the prevalence of epilepsy in older people.

There is now a spectral perception of epilepsy as more than a tendency to recurrent seizures. At one end, epilepsy is regarded as a pervasive brain disorder, with significant comorbidities such as migraine, depression, intellectual disability and dementia. Conversely, one emerging view is that epilepsy is also a systemic disorder with a preponderance of neurological features but not exclusively so; auto-immune diseases, cardiorespiratory and gastrointestinal disease are all significantly over-represented in people with epilepsy (Seidenberg et al, 2009, AWC Yuen et al, 2018, Keezer et al, 2016, Shlobin et al, 2021). Thus, 'extra-neuronal' systemic and physiological factors, exacerbated with ageing, may also play a role in epileptogenesis and enduring seizure freedom in later years.

5.Conclusion

Terminal seizure-freedom after long-standing DRE is attained in a cohort of people, raising fundamental questions about the neurobiology of epilepsy and its intersection with ageing, natural and pathological. Future research aimed at creating models to explore epilepsy in the ageing brain may provide valuable mechanistic insights, identify potential biomarkers of seizure freedom and help guide future therapies.

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TABLE 1. Demographics of the cohort (yr = years).

Variable	Number	Median (Range)
Age at death (yr)	226	65 (19-103)
Age at onset (yr)	212	7 (0-56)
Duration of epilepsy (yr)	212	52 (2-88)
Time of follow-up (yr)	226	29 (0.25-73)
Cumulative length of previous periods of seizure-freedom (yr)	35	4 (2-28)
Age at terminal seizure-freedom (yr)	39	68 (33-93)
Length of last period of seizure-freedom (yr)	39	7 (2-41)
Number of ASM tried	226	4 (2-14)

TABLE 2. Clinical characteristics of the cohort

Gender	**Number (%)**
Male	148 (65)
Female	78 (35)
Syndrome	
Idiopathic Generalised Epilepsy	10 (4)
Cryptogenic	120 (53)
Symptomatic	96 (42
Status epilepticus	
Yes	46 (20)
No	180 (80)
Pattern of epilepsy	
Continuous	191 (85)
Relapsing-remitting	35 (15)
Seizure frequency	
<1 seizure per month	52 (23)
1-4 seizures per month	106 (47)
>4 seizures per month	68 (30)
Intellectual disability	
Yes	56 (25)
No	170 (75)
Psychiatric comorbidity	
Yes	67 (30)
No	159 (70)
Epilepsy type	
Focal	201 (89)
Generalised	16 (7)
Unclear	9 (4)

TABLE 3 Predictors of terminal seizure-freedom in univariate and multivariate analysis

		Univariate		Multivariate		
		OR	**95% C.I.**	**OR**	**95% C.I.**	**p Value**
Age at death		1.1	1.06, 1.14	1.09	1.05, 1.13	< 0.0001
Aetiology (compared with cryptogenic)						
	Symptomatic aetiology	0.45	0.21, 0.95			
	Idiopathic aetiology	0.38	0.05, 3.16			
Psychiatric history		0.38	0.15, 0.94			
Status epilepticus		0.28	0.08, 0.95			
Seizure frequency (reference group <1/month)						0.0005
	> 4 seizures per month	0.22	0.10, 0.49	0.27	0.11, 0.62	
	1-4 seizure per month	0.04	0.01, 0.19	0.10	0.02, 0.47	

Backward stepwise logistic regression. R square: Hosmer and Lemeshow 0.539, Cox & Snell 0.250, Nagelkerke 0.416. Model $\chi 2 = 65.145$, $p < 0.0001$; C.I. = confidence interval.

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