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Premature mortality in refractory partial epilepsy: does surgical treatment make a difference?

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ABSTRACT

Background Epilepsy carries an increased risk of premature death. For some people with intractable focal epilepsy, surgery offers hope for a seizure-free life. The authors aimed to see whether epilepsy surgery influenced mortality in people with intractable epilepsy.

Methods The authors audited survival status in two cohorts (those who had surgery and those who had presurgical assessment but did not have surgery).

Results There were 40 known deaths in the non-surgical group (3365 person years of follow-up) and 19 in the surgical group (3905 person-years of follow-up). Non-operated patients were 2.4 times (95% CI 1.4 to 4.2) as likely to die as those who had surgery. They were 4.5 times (95% CI 1.9 to 10.9) as likely to die a probable epilepsy-related death. In the surgical group, those with ongoing seizures 1 year after surgery were 4.0 (95% CI 1.2 to 13.7) times as likely to die as those who were seizure-free or who had only simple partial seizures. Time-dependent Cox analysis showed that the yearly outcome group did not significantly affect mortality (HR 1.3, 95% CI 0.9 to 1.8).

Conclusion Successful epilepsy surgery was associated with a reduced risk of premature mortality, compared with those with refractory focal epilepsy who did not have surgical treatment. To some extent, the reduced mortality is likely to be conferred by inducing freedom from seizures. It is not certain whether better survival is attributable only to surgery, as treatment decisions were not randomised, and there may be inherent differences between the groups.

INTRODUCTION

Some patients with intractable focal seizures are candidates for surgical treatment, which may be curative. We assessed the survival of patients who had surgery at the National Hospital for Neurology and Neurosurgery (NHNN) and of patients who were evaluated for epilepsy surgery but in whom surgery was not performed.

METHODS

Surgical cohort

A prospective epilepsy surgery register has been kept at NHNN since 1989 for continuing audit. At annual follow-up, the seizure outcome group for the previous 12 months is recorded using the ILAE epilepsy surgery outcome scale.[1] Patients in group 1 are completely seizure-free, and those in group 2 may have 'auras.' Groups 3–6 have increasingly more seizures. In the analyses we considered those in groups 1 and 2 as 'seizure-free,' to enable comparison with other published cohorts. The duration of follow-up was estimated from the date of surgery and the date of death, or the date last known to be alive.

Non-surgical cohort

A register is also kept of patients evaluated for epilepsy surgery. Those who did not have surgery included those deemed unsuitable after investigations, those who declined, those who died before surgery and those who were still awaiting surgery. Individual follow-up was obtained. The duration of follow-up was calculated from the time of initial presurgical evaluation until the date of death, or the date at which each patient was known to be alive.

ANALYSIS

Person-years of follow-up were estimated for the two groups. The age and duration of follow-up were compared using the Kruskal–Wallis test. Age at time of surgery or investigation (non-operated group) was divided into five groups (<25 years, N=221; 25–29 years, N=251: 30–34 years, N=225; 35–41 years, N=255; ≥42 years, N=249). Age was unknown for one patient.

Those who had surgery were divided into groups based on seizure outcome group at the first year after surgery and when last seen (outcome group 1 or 2, outcome group 3–6). Patients were further grouped according to whether they remained seizure-free (outcome group 1 or 2) or not seizure-free (outcome group 3–6) throughout follow-up, or whether they moved between these two groups.

Cox regression analysis was performed comparing total mortality, epilepsy-related death and sudden unexplained death in epilepsy (SUDEP) in those who had surgery with those who did not, and comparing mortality in those seizure-free (group 1 or 2) with those not seizure-free at first year after surgery and at last contact. The strength of relationship was estimated by HRs and 95% CIs; a 95% CI which excludes 1.00 indicates a statistically significant result.

Cox regression was performed to compare those with variable outcome (varying between seizure-free and not seizure-free) and those with seizures throughout follow-up with those seizure-free (group 1 and 2) throughout follow-up. A Cox-model with time-dependent covariates (with an interaction term between year and outcome class) was used to assess the influence of seizure recurrence on mortality.

Analysis was performed in Stata MP/10.

This audit was approved by the Joint Ethics Committee of NHNN and the Institute of Neurology.

RESULTS

Patients

The non-surgical patients were slightly older than the surgical patients and had a shorter median length of follow-up (table 1).

Those with surgery were aged between 16 and 64 years. The maximum follow-up was 17.4 years. In 30 people, follow-up was less than 0.8 years; six died (two of SUDEP, one of cancer, one from a non-epilepsy-related accident, one of suicide and one of infection). An additional 16 people have no outcome groups. In 46 patients, we have only one outcome group; two died, both of cancer.

The pattern of outcome groups and deaths for the remaining patients is shown in table 2.

The non-surgical group were aged 15–71 years. Twenty-five patients (3.9%) had no recorded follow-up (some live overseas) and are excluded from the analysis. The maximum follow-up duration is 15.4 years. Of the 40 (6.2%) known deaths, 20 died of SUDEP, two of possible SUDEP, one drowned, one died in status, one committed suicide, three died of cancer, five died of other unrelated conditions, and in seven the cause of death was unknown to us.

We classified those dying of SUDEP, drowning and status as having probable epilepsy-related deaths (N=24 for the non-surgical group and 7 for the surgical group).

Survival in the non-surgical and surgical patients

Those who did not have surgery were more than twice as likely to die during follow-up (HR 2.5; 95% CI 1.5 to 4.4). Neither gender nor age affected the analysis (HR adjusted for age group and gender 2.4, 95% CI 1.4 to 4.2). Age group did not affect outcome independently, although gender affected the outcome on a time-dependent basis.

Those in the non-surgical group were more likely to die from a probable epilepsy-related death than those in the surgical group (HR 4.6; 95% CI 1.9 to 11.0); this was unaffected by gender or age group (adjusted HR 4.5, 95% CI 1.9 to 10.9). For SUDEP and possible SUDEP, HR=4.1 (95% CI 1.7 to 9.9).

Survival by seizure outcome class in surgical patients

Patients with a follow-up of less than 0.8 years (including six who died) and those with unknown outcome are excluded from the subsequent analyses which are dependent on the seizure outcome group. At the end of the first year, 369 were in outcome group 1 or 2 (four deaths), and 146 were in outcome group 3–6 (nine deaths); those in outcome group 3–6 were 4.8 (95% CI 1.5 to 15.9) times as likely to die as those in group 1 or 2. This was affected only slightly by gender or age group at surgery (adjusted HR 4.0, 95% CI 1.2 to 13.7). At last review, 365 were in outcome group 1 or 2 (six deaths) and 150 in group 3–6 (seven deaths).

Table 1 Patient demographics

	Non-surgical	Surgical	p Value
N (males)	641 (309)	561 (262)	
Median (IQR) age at operation or assessment in years	33.4 (27.3 to 41.2)	31.9 (26.4 to 39.0)	0.02
Median (IQR) follow-up in years	5.0 (2.6 to 8.4)	6.8 (3.1 to 10.7)	0.0001
Total follow-up (years)	3365	3905	
Deaths	40 (1 in 84 years)	19 (1 in 206 years)	
Epilepsy-related deaths	24 (1 in 140 years)	7 (1 in 558 years)	

Table 2 Causes of death in patients according to common patterns of outcome

Pattern	N	Deaths	Cause of death
Constant outcome: seizure-free	209	2	Cancer (2)
Constant outcome: never seizure-free	61	4	Cardiac failure, SUDEP (3)
Initially seizure-free, then seizures	44	1	Cancer
Initially seizures, then seizure-free	58	3	Cardiac problems, unknown, SUDEP
Initially and finally seizure-free, with seizures intervening	34	0	
Complex pattern: never seizure-free	21	1	SUDEP
Complex pattern, including seizure freedom	42	0	
Total	469	11	

In the fifth group (initially and finally seizure-free, with seizures intervening) the transient seizures were frequently caused by stopping AEDs, or by another temporary precipitant.
Seizure-free: outcome group 1 or 2; seizures: outcome groups 3–6.
SUDEP, sudden unexplained death in epilepsy.

Those in outcome group 3–6 were 2.3 (95% CI 0.8 to 6.9) times as likely to die as those in group 1 or 2.

Throughout follow-up, 287 remained in group 1 or 2 (three deaths), 94 remained in group 3–6 (six deaths) and 134 moved between those two groups (four deaths); those consistently in group 3–6 were 4.9 (95% CI 1.2 to 20.3) times as likely to die as those remaining in group 1 or 2. The HR became non-significant after adjustment for age-group and gender (adjusted HR 4.0 (95% CI 0.97 to 16.6)).

The time-dependent Cox analysis showed a weak relationship between yearly outcome group and mortality which did not reach statistical significance (HR 1.29, 95% CI 0.93 to 1.8). The interaction term was not significant (p=0.8), showing no evidence that the mortality risk varied with time.

No analysis was performed within the surgical group for epilepsy-related deaths, as only five such deaths occurred in people with seizure outcome data (table 2).

DISCUSSION

We found that those with refractory focal epilepsy who had surgery had a lower risk of premature death than those who did not. Short-term follow-up of epilepsy surgery generally shows a beneficial effect.[2–5] Seizure status is not always constant over time,[3 4 6–12] and this may affect mortality.

In a randomised controlled trial, 80 patients with temporal lobe epilepsy were randomised to surgical or medical treatment for 1 year; the only death was SUDEP in a medically treated patient.[13] Another study matched 201 surgical patients with 185 retrospective controls and found no difference in survival, even in a subgroup of 38 patients with controls who could have been surgical candidates.[14] In common with other studies, we found that those who did not have surgery had shorter survival times than those who did[15 16]

Our results are similar to a study in surgical patients which reported three deaths in 148 patients who were seizure-free (Engel class I) throughout follow-up and eight deaths in 67 patients not seizure-free.[17] Another study reported one death in 258 patients with no recurrences and 18 deaths in 325 people with recurrences.[18]

Those with a poor outcome at 1 year were more likely to die than those with good outcome. The outcome group at last follow-up, however, seemed less likely to predict death. No analysis was performed using three groups (non-surgical, surgical with good outcome and surgical with poor outcome), as

six deaths in the surgical group would be discounted (as death occurred before an outcome group was defined) leading to bias. Time-dependent analysis showed that the relationship between outcome group and mortality was weak, with no evidence at all that this varied with time. The lack of significance of the last outcome group and of the time-dependent analysis may be related to the small number of deaths (13). Despite a long follow-up, the power is limited by the small numbers of deaths and hence large HRs.

One limitation is the difference in follow-up between the groups. Cox regression, however, makes allowance for incomplete follow-up, with those who are 'lost' being followed up to the time at which they were last known to be alive.

Many epilepsy-related causes of death are more common in people with higher seizure frequencies,[19] and surgery is frequently successful in abolishing seizures. Some of the difference in mortality between those suitable for surgery and those not, and between those who have good seizure outcome and those who do not, however, may be due to intrinsic differences in the patients and their epilepsies, rather than the effects of surgery.[20 21]

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Competing interests None.

Ethics approval Ethics approval was provided by the Joint Ethics Committee of Institute of Neurology and National Hospital for Neurology.

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