

The impact of epilepsy surgery on mortality

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ABSTRACT – Patients with refractory epilepsy suffer from an increased risk of death, primarily due to seizure-related fatalities including sudden unexpected death (SUDEP), which could be conceivably avoided by surgical cure of the epilepsy. Several series have addressed this issue by comparing the mortality rate between medically and surgically treated drug resistant populations, as well as between patients, seizure free and non seizure free post-operatively. Results from some studies suggest that successful temporal lobe surgery reduced the risk of death to that observed in the normal population, whereas patients who continue to suffer recurrent seizures still present an increased standardized mortality ratio (SMR). However, other series have failed to replicate this finding, or found no difference in the overall mortality and SUDEP rates between operated and medically treated patients. All the above studies suffer various types of methodological limitations, hampering any definite conclusion regarding the impact of epilepsy surgery on mortality. However, part of the apparently discordant reported findings might be reconciled through the following framework. Patients who will eventually respond favourably or unfavourably to an anterior temporal lobectomy might already differ in the risk of seizure-related death, pre-operatively. Specifically, patients whose temporal lobe epileptogenic network extends to the perisylvian region (temporal plus epilepsy) appear to be at higher risk of failed TLE surgery, secondary generalised tonic-clonic seizures, ictal apnoea or insula-driven severe cardiac arrhythmias. This population might carry most of the SUDEP burden, both pre- and post-operatively, accounting for the lack of an obvious net reduction of seizure related deaths after temporal lobe surgery. A multicentric study has recently been launched in order to test this hypothesis, and will hopefully help to conclude on the impact of epilepsy surgery on mortality outcome.

Key words: epilepsy, surgery, mortality, SUDEP, insula

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General aspects of mortality in epilepsy

Patients with epilepsy suffer a two to three-fold increase in mortality as compared to the general population, resulting in a standardized mortality ratio (SMR) of 2 to 3 (Cockerell 1996, Tomson 2000). The causes of death fall into three main categories: i) deaths apparently unrelated to the epileptic condition or its underlying pathology, such as extra-cerebral tu-

mours or cardiovascular diseases, which age and sex dependant incidence might however be increased in epileptic patients (White *et al.* 1979, Annegers *et al.* 1984, Klenerman *et al.* 1993, Annegers 1997a, Lhatoo *et al.* 2001); ii) deaths related to the aetiology of the seizure disorder, which are the most frequent in population-based studies (Cockerell 1996, Gaitatzis *et al.* 2004, Tomson *et al.* 2005); and iii) epilepsy related deaths, which mechanisms include seizure-induced

accidents, status epilepticus, and sudden unexpected deaths (SUDEP). This third category accounts for 6% to 40% of all deaths reported in epilepsy cohorts (Forsgren *et al.* 1996, Loiseau *et al.* 1999, Shackleton *et al.* 1999, Opeskin *et al.* 2000, Tomson 2000, Lhatoo *et al.* 2001, Walczak *et al.* 2001, Camfield *et al.* 2002), whereas it represents the majority of deaths observed in drug resistant epilepsy. Suicide was also found to be six fold more frequent in epileptic patients than in the general population (Rafnsson *et al.* 2001).

SUDEP is an unexpected, but no more unexplained, death in epilepsy

The relation between SUDEP and the occurrence of seizures has been clearly established in the minority of witnessed cases (Terrence *et al.* 1975, Leestma *et al.* 1989, Lip and Brodie 1992, Langan *et al.* 2000, Opeskin *et al.* 2000). In addition, various studies have demonstrated that SUDEP is more likely to occur in epileptic patients with poor seizure control and generalized tonic-clonic seizures (GTCS) (Langan 2000, Opeskin *et al.* 2000, Walczak *et al.* 2001, Strauss *et al.* 2003). Various ictal, post-ictal, pathological, and experimental data alternatively favour the primary role of respiratory failure (Terrence *et al.* 1981, Coulter 1984, Leestma *et al.* 1989, Singh *et al.* 1993, Johnston *et al.* 1995, 1997, Nashef *et al.* 1996, Simon 1997, Walker and Fish 1997, Langan *et al.* 2000, So *et al.* 2000), or of cardiac dysfunction (Blumhardt *et al.* 1986, Oppenheimer *et al.* 1991, Jallon 1997, Tigarani *et al.* 1997, 2003, Natelson *et al.* 1998, Tinuper *et al.* 2001, Rocamora *et al.* 2003, Nei *et al.* 2004), suggesting that both mechanisms might contribute to SUDEP (Earnest *et al.* 1992).

Mortality in drug resistant epilepsy

Death rate, SUDEP incidence, and SMR are significantly higher in patients with drug resistant epilepsy than in those well controlled by AEDs. However, available data derived from very heterogeneous clinical settings including: anti-epileptic drugs (AEDs) add-on trials (Leppik 1995, Leestma *et al.* 1997, Racoosin *et al.* 2001), vagus nerve stimulation (VNS Therapy) trials (Annegers *et al.* 1998), drug resistant epilepsy cohorts (Klenerman *et al.* 1993, Nashef *et al.* 1995a, 1995b, Derby *et al.* 1996), pre-surgical evaluation programs (Dasheiff 1991, Vickrey *et al.* 1995, Nilsson *et al.* 2003), and operated patients with post-operative seizure recurrence (Sperling *et al.* 1999, Salanova *et al.* 2002, Nilsson *et al.* 2003). Important differences in age, epilepsy duration, seizure type and seizure frequency, are likely to distinguish these various populations and to account for the observed variability in death rates and SMR. For instance, death rates are more elevated in older population (33.3/1000 patient-years in a series of patients whose

mean age was 52, as compared to 6.3/1000 patient-years in school-aged children and adolescent), while the SMR follows an opposite trend (1.9 and 15.9 in the two previous series, respectively) due to the age related increased mortality rate in the control population used for calculating SMR (Klenerman *et al.* 1993, Nashef *et al.* 1995b). SUDEP incidence appears to be less variable among series than the overall death rate and SMR though still varying from 2.2 to 9/1000 patient-years. In a review pooling data from all series providing detailed numbers of SUDEP and patient-years of follow-up, we found a total of 154 SUDEP among 41439 person-years, resulting in a mean SUDEP incidence of 3.7/1000/year (Ryvlin and Kahane 2003). More recently, a meta-analysis of 36 studies concluded that the four main predictors of SUDEP were an age between 15 and 30 years old, a monthly seizure frequency above 15, a treatment combining more than two AEDs, and a duration of epilepsy above 15 years (Tellez-Zenteno *et al.* 2005). Seizure type, and in particular the occurrence of GTCS, also represents an important risk factor of SUDEP (Langan 2000, Opeskin *et al.* 2000, Walczak *et al.* 2001, Strauss *et al.* 2003).

Impact of epilepsy surgery on mortality and seizure-related deaths

The impact of epilepsy surgery on mortality has been evaluated in several series (Guldvog *et al.* 1991, Vickrey *et al.* 1995, Hennessy *et al.* 1999, Sperling *et al.* 1999, Salanova *et al.* 2002, Nilsson *et al.* 2003, Radhakrishnan *et al.* 2005, Stavem and Guldvog 2005, Salanova *et al.* 2005). Three of these series have concentrated on temporal lobe surgery and demonstrated that the post-operative mortality rate was normal in seizure free patients, whereas it was significantly higher, and comparable to that observed in drug resistant epilepsy cohorts, in patients who failed surgery (Sperling *et al.* 1999, Salanova *et al.* 2002, 2005). This result suggests that successful surgery reduces the risk of epilepsy-related death, dramatically. However, this conclusion which has not been tested directly, relies on the assumption that patients whose seizures were controlled by surgery had a pre-operative increased mortality rate comparable to that of patients who ultimately failed surgery.

This assumption remains disputable, however, in as much as the reasons for surgical failure in TLE are not fully understood. In fact, clinical predictors of unfavourable post-operative seizure outcome might also be associated with a higher risk of death, pre-operatively. For instance, secondary generalized seizures represent a risk factor for both SUDEP and surgical failure in TLE (Blume *et al.* 1994, Specht *et al.* 1997, Langan 2000, Opeskin *et al.* 2000, Walczak *et al.* 2001, Strauss *et al.* 2003). In addition, other series could not confirm the above findings, and found comparable death rates in patients with and without post-

operative seizure relapse (Hennessy *et al.* 1999, Nilsson *et al.* 2003).

Another way to look at the impact of epilepsy surgery on mortality, is to compare cohorts of surgically and medically treated patients. Five studies have addressed this issue, using various methodologies, and again providing controversial results (Guldvog *et al.* 1991, Vickrey *et al.* 1995, Nilsson *et al.* 2003, Radhakrishnan *et al.* 2005, Stavem and Guldvog 2005). Only one of these series reported a significantly lower death rate in operated patients as compared to those medically treated (Vickrey *et al.* 1995). However, this result could be partly explained by pre-operative differences between the two populations, including the type of epilepsy (mainly non-localized in the medical group and temporal in the operated patients) and the baseline seizure frequency which was significantly higher in the non operated patients (Vickrey *et al.* 1995). The other four series failed to demonstrate a difference in mortality between operated and non operated patients (Guldvog *et al.* 1991, Nilsson *et al.* 2003, Radhakrishnan *et al.* 2005, Stavem and Guldvog 2005).

It is apparent from the above studies that no consensus emerges regarding the impact of surgery on mortality. As already pointed out, several differences in methodology, type of control population and surgical candidates, are likely to explain the discordant findings observed in the literature. Taking all available data into account, it appears that the main result which might hold on is the lower risk of seizure-related death in seizure free patients after temporal lobe surgery, as compared to those who failed to respond to this surgical procedure. Whether this finding reflects the impact of surgery proper, pre-operative biological differences between "surgically resistant" and "surgically sensitive" TLE patients, or both phenomena, remains an open question. The second possibility, ie that of higher pre-operative death rate in patients who will eventually fail to respond to temporal lobe surgery as compared to the other patients, would elegantly reconcile the positive findings reported in temporal lobe surgery series and the negative results of studies which have compared surgically and medically treated patients. Testing this hypothesis remains elusive at the present time, since we cannot precisely anticipate the post-operative seizure outcome prior to surgery. However, recent progress in our understanding of surgical failures might provide some clues to address this issue (Ryvlin and Kahane 2005).

Bridging the gap between temporal lobe surgery failures and SUDEP

Concept of temporal plus epilepsy

Surgical failures are thought to usually result from an incomplete removal of the epileptogenic zone (Ryvlin and

Kahane 2005, Salanova *et al.* 2005), as illustrated by the very poor results of palliative temporal lobe surgery (Wieser *et al.* 1990, Fish *et al.* 1991, Li *et al.* 1997, 1999), and by the 50% rate of class 1 outcome obtained after re-operation to remove a hippocampal remnant (Germano *et al.* 1994, Hennessy *et al.* 2000, Schwartz *et al.* 2001). Conversely, bi-temporal seizures seem to account for less than 20% of surgical failures in TLE (Hennessy *et al.* 2000). Following the pioneering work of Claudio Munari (Munari *et al.* 1980, Munari and Bancaud 1992, Munari *et al.* 1995a), we have developed the concept of temporal-plus epilepsy as representing a major source of temporal surgery failures (Kahane *et al.* 2001a, Ryvlin *et al.* 2001, Ryvlin 2003, Ryvlin and Kahane 2005). Temporal-plus epilepsy, which we have identified in roughly 20% of 176 TLE surgical candidates, refers to an epileptogenic zone that primarily encompasses the temporal lobe but extends outside the boundary of a standard resection. The epileptogenic zone might extend to the most posterior aspect of the temporal lobe up to the temporo-parieto-occipital junction, to the orbital frontal and frontal basal structures, or to the peri-sylvian region, including the insula as well as the frontal and parietal operculum (Munari *et al.* 1980, Munari and Bancaud 1992, Munari *et al.* 1995a, Isnard *et al.* 2000, Kahane *et al.* 2001a, Ryvlin 2003). Since the temporal lobe is primarily involved in temporal-plus epilepsy, electro-clinical and MRI findings are often suggestive of TLE, including signs of hippocampal sclerosis (Kahane *et al.* 2001b, Ryvlin *et al.* 2001). In addition, the stimulation of the insular cortex has proved to elicit vegetative symptoms comparable to those observed during a mesial temporal stimulation or discharge (Ostrowsky *et al.* 2000).

Though the sequence in ictal semiology and the spatial distribution of scalp-EEG discharge might provide some hints towards the possibility of temporal-plus epilepsy, the latter can only be demonstrated by intra-cranial EEG recordings, using an appropriate placement of electrodes. Thus, at the present time, most patients with temporal plus epilepsy who fulfil the criteria used to defined the mesial temporal lobe epilepsy syndrome, will be identified as TLE patients, and might eventually undergo a standard anterior temporal lobectomy or amygdalo-hippocampectomy. In our experience, these surgical procedures are ineffective in over 90% of patients with temporal plus epilepsy (Ryvlin *et al.* 2001). The possibility that an important proportion of patients who failed temporal lobe surgery might have an epileptogenic zone extending to extra-temporal structures, including the insula and the fronto-opercular region might be relevant to the suspected mechanisms of SUDEP.

Ictal arrhythmia and cardiogenic SUDEP

The incidence of high risk arrhythmias and cardiac asystole were thought to be very low, based on data obtained

during standard video-EEG monitoring (Keilson *et al.* 1987, Scott and Fish 2000).

However, a recent long term EKG study, using an implantable loop recorder in 20 patients with drug resistant partial epilepsy, showed that paroxysmal high risk arrhythmia necessitating a permanent pacemaker insertion could be detected in 20% of cases (Rugg-Gunn *et al.* 2004). SUDEP patients also suffer greater ictal tachycardia than a matched population of refractory patients, in particular during nocturnal seizures (Nei *et al.* 2004). Accordingly, abnormal heart rate variability appears to be more pronounced during sleep and epileptiform discharges (Ferri *et al.*, 2002, Zaatreh *et al.* 2003, Nei *et al.* 2004), as well as in poor candidates for anterior temporal lobectomy (Frysinger *et al.* 1993).

The role of the insular cortex in cardiovascular function has been well demonstrated in animals and humans (Ruggiero *et al.* 1987, Oppenheimer and Cechetto 1990, Oppenheimer *et al.* 1990, 1992a). In man, left insular strokes are associated with alterations of cardiac autonomic tone (Oppenheimer *et al.* 1996). More generally, insults to the insular cortex are believed to participate to cerebrogenic sudden death (Cheung and Hachinski 2000). In a recent series of five patients with seizure-induced cardiac asystole, a direct or indirect participation of the left insular cortex was suspected in 60% of cases, mainly based on the presence of MRI or SPECT abnormalities (Rocamora *et al.* 2003). Ictal bradycardia has also been observed in a patient with a right insular cortical dysplasia (Seeck *et al.* 2003).

However, the great majority of patients who were reported to exhibit ictal arrhythmias, including sinus or sinoatrial arrest, asystole, atrioventricular block, bradycardia, and ventricular fibrillation, suffered from temporal lobe seizures (Pritchett *et al.* 1980, Gilchrist 1985, Blumhardt *et al.* 1986, Dasheiff and Dickinson 1986, Kiok *et al.* 1986, Smaje *et al.* 1987, Jacome and Seropian 1988, Howell and Blumhardt 1989, Constantin *et al.* 1990, Joske and Davis 1991, Wilder-Smith 1992, Liedholm and Gudjonsson 1992, Van Rijckevorsel *et al.* 1995, Reeves *et al.* 1996, Devinsky *et al.* 1997, Iani *et al.* 1997, Jallon 1997, Lim *et al.* 2000, Tinuper *et al.* 2001, Nei *et al.* 2004). Because the insula was never investigated in these patients, and no indication was provided regarding the efficacy of a temporal lobectomy, it remains difficult to conclude on the respective role of the temporal and insular cortices in generating ictal arrhythmias. This issue is complicated by the fact that almost all temporal lobe seizures will eventually spread to the insula (Isnard *et al.* 2000). Other brain structures involved in temporal plus epilepsy might participate to ictal arrhythmias, including the orbito-frontal cortex (Munari *et al.* 1995b). Ictal bradycardia has also been reported in patients with fronto-temporal epileptic network (Constantin *et al.* 1990, Saussu *et al.* 1998, Kahane *et al.* 1999, Tinuper *et al.* 2001).

Central and obstructive apnoea in SUDEP

A primary respiratory dysfunction appears likely to account for an important proportion of SUDEP (Nashef 1997), as suggested by the frequent observation of pulmonary oedema at pathology (Terrence *et al.* 1981, Leestma *et al.* 1989, Earnest *et al.* 1992). Both central and obstructive apnoea can occur during or immediately after a seizure, the former being more frequent than the latter (Coulter 1984, Singh *et al.* 1993, Nashef *et al.* 1996, So *et al.* 2000). These respiratory changes can be followed by ictal bradycardia, leading to the possibility that part of the reported seizure-related arrhythmias were consecutive to ictal apnoea (Nashef *et al.* 1996). Obstructive apnoea will usually complicate a generalized tonic-clonic seizure, whereas central apnoea might occur during both partial and generalized seizures (Nashef *et al.* 1996). The majority of published cases of ictal central apnoea were reported to suffer temporal lobe seizures (Coulter 1984, Singh *et al.* 1993, Nashef *et al.* 1996), without confirmatory intra-cranial EEG or post-operative data. Temporal plus epilepsies, and in particular those involving the frontal operculum region, might be associated with a higher risk of potentially lethal respiratory failures than TLE, by favouring GTCS as well as central apnoea. Indeed, electrical stimulation of the rolandic area has proved to elicit apnoea (Penfield and Jasper 1954), whereas the association of an early and intense frontal operculum ictal discharge, together with a temporal lobe seizure, will promote secondary generalization. Accordingly, GTCS represents a risk factor for surgical failure in TLE, as well as for SUDEP (Blume *et al.* 1994, Specht *et al.* 1997, Langan 2000, Opeskin *et al.* 2000, Walczak *et al.* 2001, Strauss *et al.* 2003). It should be noted that GTCS also favoured EKG abnormalities (Nei *et al.* 2000).

Conclusion

Important biological differences are likely to distinguish patients with apparent TLE who will eventually fail surgery from those who will remain seizure-free post-operatively. These differences, which could include the involvement of the insula and frontal operculum within the epileptogenic network, and an increased likelihood of developing secondary generalization as well as ictal or post-ictal apnoea or arrhythmia, might explain part of the difference in standardized mortality rate (SMR) observed between cured and non cured operated patients, as well as between operated patients and those who were refused surgery. One possibility to test this hypothesis would be to correlate the mortality rate to a combination of parameters that best predict the post-operative seizure outcome, in a large cohort of patients entering a presurgical evaluation program. However, the robustness of available clinical predictors might not be sufficient to ensure an appropriate

statistical power, provided the incidence of SUDEP in the population studied.

Another possibility would be to compare the death rate of TLE patients whose pre-surgical workup has enabled to exclude a temporal plus epileptogenic zone to that of patients with a well ascertained temporal plus epilepsy. A multicentric French study has recently been launched to tackle this issue.

In any event, seizure-related accidental deaths can occur in any type of epilepsy, including surgery sensitive TLE, so that controlling seizures should reduce the number of such deaths. From that perspective, epilepsy surgery appears likely to have a positive impact on mortality, even when taking into account the very low risk of surgically-related fatalities. Whether or not that impact have been overestimated, remains the only critical issue. □

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