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Refractory epilepsy is a life-threatening disease: Lest we forget

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Refractory epilepsy is a life-threatening disease

Lest we forget

It has long been known that premature mortality is increased on average 2- to 3-fold in epilepsy compared to the general population. Premature mortality in those with epilepsy is often attributed to its underlying etiology (especially structural-metabolic causes); however, epilepsy-related causes such as status epilepticus and sudden unexpected death in epilepsy (SUDEP), along with comorbidities, are substantial contributors to epilepsy-related mortality. The highest mortality occurs in individuals with drug-resistant epilepsy, suggesting that seizure control is an important approach to reduce the risk of premature death.

Resective epilepsy surgery is highly effective in carefully selected patients, as demonstrated in 2 randomized controlled trials for temporal lobe epilepsy, and in hundreds of surgical cohort studies. Epilepsy surgery is cost-effective, is associated with an improvement in psychosocial outcomes, and carries a low overall frequency of complications. Despite its high efficacy, authorities suggest that fewer than 1% of patients with drug-resistant epilepsy are referred to epilepsy centers that offer surgery, and delays to epilepsy surgery of over 20 years exist for the few who are referred. Indeed, there has been no improvement in delays to referral since the American Academy of Neurology published a Practice Parameter declaring surgery the treatment of choice for drug-resistant temporal lobe epilepsy.

In this issue of Neurology®, Sperling et al. perform a reappraisal of epilepsy surgery focusing on mortality as an outcome. Although earlier studies were published by these authors on this topic, this is likely the largest clinical cohort for such an investigation, with 1,006 surgically and 104 nonsurgically treated drug-resistant patients with a follow-up time of 8,126.62 person-years between 1986 and 2013. The time period is ideal as it incorporates the full era of MRI utilization in the presurgical evaluation of those with epilepsy. Most importantly, however, this study, in view of its impressive size, allowed the authors to carefully explore factors associated with mortality that had not been adequately investigated in earlier studies, such as the site of surgical resection, postoperative seizure frequency, and seizure characteristics.

As they reported previously in a smaller cohort, the authors found that epilepsy surgery was associated with lower mortality rate (8.6 per 1,000 person-years [95% confidence interval 6.58–11.15]) than ongoing nonsurgical management (25.3 per 1,000 person-years [14.50–41.17]; p < 0.001), particularly in seizure-free patients (5.2 per 1,000 person-years [2.67–9.02]). Perhaps the most important finding is the increased mortality rate in those with ongoing generalized tonic-clonic seizures (GTCS) (>2 per year) after surgery, a finding that is not surprising, and that supports the previously described association between GTCS and mortality, including SUDEP. Mortality in this study was not influenced by the surgical resection site (temporal vs extratemporal).

Despite the many strengths of this important study by Sperling et al., including the larger population than in the majority of previously published studies, there are some limitations that must be considered, most of which are addressed by the authors. First is a lack of knowledge regarding the validity of mortality reporting in the US Social Security Death Index, especially in regards to the reporting of causes of death. In fact, the cause of death was unknown in over half of patients, precluding stratification into epilepsy-related vs non-epilepsy-related causes of death. Second, the surgical and the nonsurgical group were not matched, with the nonsurgical group having more severe epilepsy and more comorbidity, thus resulting in selection bias. In addition, the surgical group is 10 times larger than the nonsurgical group. Finally, the lack of risk adjustment for comorbidity is an important limitation, as a number of comorbidities are associated with mortality. There even exists a validated epilepsy-specific comorbidity risk adjustment index for mortality that could have been applied as part of the analysis.

Despite the above limitations, the authors are to be congratulated for tackling this important contemporary study and for enhancing our understanding of key variables associated with increased mortality rates.
in patients with drug-resistant epilepsy. The most valuable take-home messages from this study are as follows: (1) seizure freedom is a major determinant of survival in people with epilepsy; and (2) every effort should be made to control GTCS in particular. This emphasizes the overriding necessity of controlling disabling seizures in all patients with epilepsy, whether they are surgical candidates or not.

As health professionals, it is our duty to provide the best evidence-based care. It is clear that seizure freedom is a critical goal for reducing the risk of premature death in our patients. It is our responsibility to ensure that patients who continue to have disabling seizures, despite 2 appropriate trials of antiseizure medication, are referred to a full-service epilepsy center, one that not only offers surgery, but also other specialized diagnostic and therapeutic approaches that could abolish disabling seizures. In view of rapid advances in epilepsy diagnosis and treatment, both surgical and nonsurgical, it is recommended that re-referral be considered regularly, according to the latest American Academy of Neurology quality measures statement.

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