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Who will use epilepsy surgery nomograms, and why?

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Author
Jr, EJ

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See Articles page 283

Advances in neurodiagnostic technology and microsurgery have greatly improved the safety and efficacy of surgical treatment for epilepsy in recent years.[1] Results from two randomised controlled trials have shown the superiority of surgical treatment over continued drug treatment for patients with medically refractory temporal lobe epilepsy.[2,3] A practice parameter produced by the American Academy of Neurology recommended surgery as the treatment of choice for this type of epilepsy, and acknowledged that similar results could be obtained for drug-resistant neocortical epilepsy.[4] More recent studies have shown that surgical benefit is long-lasting for most patients,[5] and that surgical mortality and complications are rare.[6] Nevertheless, surgical treatment for epilepsy remains one of the most underused accepted therapeutic interventions in medicine. It has been estimated that less than 1% of all patients in the USA who meet the International League Against Epilepsy criteria for drug-resistant epilepsy—persistence of disabling seizures despite two appropriate antiseizure drug treatments—are referred to epilepsy centres, where candidacy for surgery can be ascertained.[7] In fact, referral to epilepsy centres in the past several decades has decreased,[8] and the average duration of epilepsy for those who are referred for surgery has increased to more than 20 years,[9] often too late to avoid irreversible disability. The first randomised controlled trial[2] and the American Academy of Neurology practice parameter[4] seem to not have stimulated earlier referrals.[10]

In an effort to improve identification of potential candidates for surgery, Lara Jehi and colleagues constructed two nomograms to predict surgical outcome based on information collected from 846 patients before referral to the Cleveland Clinic (Cleveland, OH, USA). They validated these results with data collected from 604 patients before referral to four other epilepsy centres in Europe, Latin America, and the USA.[11] They conclude that these nomograms could be an innovative and practical instrument for individualised prediction of seizure outcome after surgical treatment for epilepsy. This work shows an increasing interest in applying statistical predictive modelling to prognosis of diseases and treatments. Although far from perfectly predictive, the nomograms seem to be a step towards the identification of patients who are most likely to benefit from surgery. Because they are based on data available before the presurgical assessment, the nomograms do not include interictal or ictal electroencephalogram, PET, ictal SPECT, magnetoencephalography, intracranial recording, or many other advanced techniques commonly used in epilepsy centres to locate an epileptogenic region. Furthermore, they do not account for the potential for surgical intervention to improve health-related quality-of-life, or the risk of such an intervention introducing an unacceptable new neurological deficit. These factors are all essential in establishing whether physicians at the epilepsy centre will recommend surgery, and whether the patient will accept this recommendation. An important question, therefore, is who will use such nomograms and for what purpose?

If such nomograms are used in epilepsy centres, they could be applied at the time of the initial visit, to help a patient who might be ambivalent about surgical treatment to decide whether or not to undergo a presurgical assessment. Alternatively, such nomograms could be widely distributed to general neurologists and primary care physicians. In this case, the nomograms could provide an important service if they indicate a high likelihood of freedom from seizures after surgery, especially if the patient and doctor had not previously considered surgery. However, a major danger of such nomograms would be the implication that patients who are judged to have a low chance of becoming seizure-free should not be referred to an epilepsy centre. Nomograms should not replace the ability of the expert epileptologist, and the detailed presurgical assessment, to make a more informed prediction of postoperative seizure outcome. Use of nomograms by general neurologists, therefore, could do a great disservice if the result is to prevent the referral of these patients to specialised epilepsy centres, not only because the patients might still be excellent candidates for surgery, but also because, even if they are not candidates for surgery, they could benefit from other treatments and approaches to psychiatric, psychological, and social management. These nomograms require prospective validation and refinement before use, but if future versions are to be distributed to non-epilepsy specialists, they should

be accompanied by a strong message that all patients who are disabled by drug-resistant seizures deserve a consultation at a specialised epilepsy centre.

Jerome Engel Jr
Department of Neurology, David Geffen School of Medicine at UCLA, 710 Westwood Plaza, Los Angeles, CA 90095-1769, USA
engel@ucla.edu

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Type 2 diabetes and cognitive function: many questions, few answers

See **Personal View** page 329

A causal association between type 2 diabetes and dementia is difficult to establish, owing to the number and complexity of possible risk factors and pathways. Candidate risk factors for dementia in patients with type 2 diabetes include those that lead to diabetes (poor lifestyle choices resulting in insulin resistance), diabetes-specific variables (hyperglycaemia, hypoglycaemia, endothelial dysfunction, inflammation, microvascular complications, and macrovascular disease), and cardiovascular risk factors that are associated with type 2 diabetes. However, the payoff from the study of this common disease association could be substantial. First, estimates of the excess risk of dementia due to type 2 diabetes are likely to underestimate the strength of the association. Many putative dementia risk factors, including the *APOE* ε4 allele, likewise increase the risk of premature mortality in diabetes,[1] and studies designed to assess competing risks have not been done. Additionally, most epidemiological research has been done in older (>70 years) patient groups, who are likely either to be long-term survivors of diabetes or to have developed diabetes at an older age, and hence to have had a fairly short duration of diabetes. Second, some of the major hypotheses that have been considered might be as relevant to the general population as to patients with diabetes. For example, the benefit of an approved antidiabetic drug that corrects insulin signalling abnormalities in a mouse model of Alzheimer's disease suggests a promising new treatment approach that could be applied generally.[2] Other pathways that might be relevant in diabetes include chronic inflammation that can prime the brain's innate immune system to increase neuroinflammation and cerebral microvascular disease, which might precipitate, add to, or act synergistically with Alzheimer's disease processes. For these reasons, type 2 diabetes could provide a model for research into pathways that lead to dementia.

In *The Lancet Neurology*, Koekkoek and colleagues[3] discuss how this research might be clinically translated. Unfortunately, a major conclusion that can be drawn from their Personal View is how little specific information is available to advise patients and clinicians. Studies of pathogenesis greatly outnumber those that address clinical problems. The available trials of glycaemic control have not shown a benefit for cognitive health, but might have been too short to detect benefit. Even less information is available about how to manage patients who have diabetes with cognitive impairment and dementia. Studies of how or when to modify complex diabetes management regimens appropriately in cognitively impaired patients would be useful given the risk of severe hypoglycaemia.[4] Safe withdrawal of selected antidiabetic medications seems to be feasible, at least in some older patient groups.[5] The symptoms of dementia associated with diabetes might differ from dementia not