MANAGEMENT OF REFRACTORY EPILEPSY

Refractory epilepsy is a distressing problem for patient and doctor.

JT BUTLER
MB ChB, FCP (SA) Neurology
Senior Specialist
Department of Neurology
Tygerberg Hospital and Stellenbosch University
W Cape

James Butler obtained the MB ChB in 1988, and the FCP (SA) Neurology in 1995. He completed a 2-year fellowship in Epilepsy and Epilepsy Surgery at the Department of Neurological Sciences, University of Western Ontario, Canada in 1996 - 1998 and obtained a certificate in Clinical Epidemiology and Biostatistics from the same university. He is currently in private practice at Constantiaberg Medi-Clinic and on the part-time staff of Stellenbosch University.

SCOPE OF THE PROBLEM

Epilepsy is common, with approximately 3% of individuals developing this disorder during a lifetime of 70 years and about 0.5 - 0.9% of the population of various countries having epilepsy at any given time. For the majority of people with epilepsy the prognosis appears favourable. Approximately 68 - 75% of individuals with epilepsy will at some stage attain freedom from seizures for at least 5 years and about 30 - 40% of patients will be free from seizures for 5 years or more and be off medication.

While these findings pre-date the generation of new anticonvulsant medications, there is no evidence that these medications have diminished the proportion of patients with medically refractory seizures. The efficacy of vagal nerve stimulation for patients with medically refractory epilepsy is equally modest.

WHY ALL THE FUSS ABOUT EPILEPSY?

Compared with someone without epilepsy, an individual experiencing epileptic seizures has an increased morbidity and mortality. For patients with medically refractory seizures health-related quality of life is often markedly impaired. Although the degree of seizure control is really an intermediate outcome, it appears to be the most important determinant of health-related quality of life. Patients with medically refractory epilepsy may endure many hardships, including prohibition from driving, stigmatisation, mood disorders, fear of seizures, sense of losing control, social isolation, lowered self-esteem, lowered rates of employment and the consequences of sustaining injuries such as burns, fractures and dislocations. Anticonvulsants during pregnancy increase the risk of congenital malformations, including various major malformations.

Although the here and now may be uppermost in the mind of an individual with epilepsy and the attending doctor, an understanding of the longitudinal aspects of epilepsy should be incorporated into therapeutic decision making. In particular, epilepsy and its treatment may have a profound impact on the psychosocial and neurodevelopmental aspects of an individual's life, especially on that of a child's. In a remarkable study of a cohort of children with epilepsy followed up for over 30 years into adulthood, Sillanpaa *et al.* demonstrated that, compared with age-matched peers in the general population, children with epilepsy are disadvantaged with regard to educational levels, vocational training, marriage or cohabitation, having children, having a driver's licence, employment status and socio-economic status.

There is some evidence that epileptic seizures may sometimes adversely affect the cognitive development of children, as evidenced by reports of children who either fail to develop or regress during periods of frequent seizures and who make considerable cognitive gains when seizures are terminated by a different anticonvulsant medication or by epilepsy surgery. Children with epilepsy have a higher prevalence of behavioural disorders than healthy children. It is unclear whether, in adults, intermittent epileptic seizures in the absence of status epilepticus may sometimes produce enduring neurological dysfunction.

There is good evidence from prospective population-based studies that individuals with epilepsy have a higher risk of dying than those without epilepsy. Much of the excess mortality is attributable to the underlying causes of epilepsy. Epilepsy-related deaths may occur as a result of accidents, drowning, status epilepticus or sudden death in epilepsy (SUDEP).

Approximately 68 - 75% of individuals with epilepsy will at some stage attain freedom from seizures for at least 5 years and about 30 - 40% of patients will be free from seizures for 5 years or more and be off medication.

For patients with medically refractory seizures health-related quality of life is often markedly impaired.

In principle, any patient with medically refractory epilepsy whose quality of life is impaired by seizures should be considered for referral.

There is very compelling evidence that a temporal lobectomy is an effective procedure, while there is reasonable evidence of the effectiveness of various other surgical procedures for epilepsy.

The cost of having epilepsy, especially intractable epilepsy, is considerable. The bulk of the costs are indirect (mainly as a result of loss of income), while medication and hospitalisation appear to consume the bulk of the direct costs. If the above consequences of seizures are to be limited, a remission from seizures should be effected as soon as possible.

WHEN IS EPILEPSY REFRACTORY?

Prognostication for individuals with epilepsy is currently an imperfect science. The majority of patients who enter remission do so during the first year after diagnosis. Late spontaneous remission of seizures occurs in a minority of patients and until such time as there are means of identifying these patients, there will be some uncertainty about the early identification of patients with a poor prognosis.

Given the multitude of causes and syndromes, epilepsy is more correctly referred to as the epilepsies. An understanding of the aetiology/syndromic classification of a patient is useful for prognostication and treatment. An epilepsy syndrome can be diagnosed at first-seizure presentation in nearly half of all patients. Individuals with seizures resulting from a pre-existing brain lesion (remote symptomatic seizures) have a lower likelihood of attaining long-term remission from seizures than patients with genetic forms of epilepsy.

In their study Kwan and Brodie found that, after the first anti-epileptic drug treatment proved ineffective for controlling epilepsy, only 11% of patients became seizure free for 1 year or more when subsequent medications were tried and only 4% of patients responded to a third drug or multiple drugs. While 1 year of freedom from seizures may not invariably predict long-term freedom from seizures, the study findings are useful in attempting to identify patients with a poor long-term prognosis.

WHO SHOULD BE REFERRED?

In principle, any patient with medically refractory epilepsy whose quality of life is impaired by seizures should be considered for referral. Seizure frequency is less important than quality of life in deciding about surgery. For example, 4 seizures per year may prevent someone from driving and working, cause embarrassment when having seizures in front of his/her family and stigmatise the person.

WHY SPECIALIST REFERRAL SHOULD NOT BE DELAYED

Patients who continue to have seizures despite being on anti-epileptic drugs require specialist referral for several reasons.

First, the diagnosis of epilepsy is commonly incorrect. Some studies indicate that up to 25% of patients with a diagnosis of medically refractory epilepsy have non-epileptic seizures. Diagnostic errors occur because a description of the event by the patient and observers cannot reliably distinguish epilepsy from non-epileptic seizures (the term 'pseudo-seizures' should be avoided since it has pejorative connotations). Non-epileptic seizures are very disabling and occur mainly in women who have had previous sexual or physical abuse. It requires early psychological therapy if the likelihood of remission is high. Such patients present with seizures and not with a history of abuse. Prolonged treatment with anti-epileptic drugs is common and studies indicate that the longer the condition remains undiagnosed, the worse the prognosis. Patients are understandably disillusioned when told that the diagnosis of epilepsy is incorrect and that they have needlessly taken medication for several and, in some instances, many years.

Second, the presence of medically refractory seizures often considerably impairs quality of life. Many years of a poor quality of life add up to a miserable existence. There may be irreversible psychosocial consequences of having epilepsy. The longer the epilepsy continues, the more likely these consequences are to endure. For instance, children who are teased and stigmatised at school may develop poor self-esteem, leave school prematurely and remain permanently disadvantaged, both psychologically and with regard to of educational status. Achieving a seizure-free outcome at the age of 24 years may never remedy the above disadvantage. An adult who stops working for 10 years because of seizures and is then rendered seizure free is at high risk of persistent unemployment (deskilling, loss of confidence, etc). Hence, if a seizure-free outcome is to be achieved, it should be as early as possible. Some individuals have epilepsy syndromes requiring specific treatment and for many others the possibility of surgery needs to be explored.

WHAT INVESTIGATIONS ARE REQUIRED BEFORE SURGERY IS CONSIDERED?

The clinical findings are complemented by prolonged video EEG recordings (in an attempt to record seizures and understand their physiology and likely origin), high-quality MRI images (Fig. 1) and neuropsychological tests. Some patients require insertion of intracranial electrodes and further video EEG recordings to localise seizures.

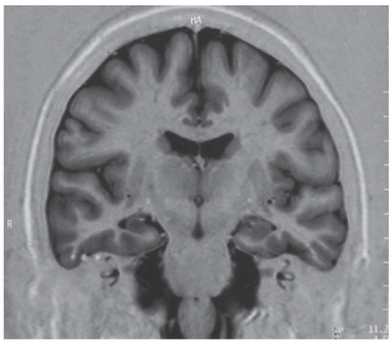

Fig. 1. Coronal inversion recovery MRI sequence – right hippocampal atrophy.

WHAT IS DONE AT SURGERY?

Surgery entails either a resection of part of the cortex deemed to be responsible for generating seizures (i.e. onset) or a disconnection of pathways responsible for propagation of seizures (i.e. spread). Resections vary in size from small corticectomies and selective amygdalohippocampectomies to anteromesial temporal lobectomies (the most commonly performed procedure) and hemispherectomies. Disconnection procedures are less commonly performed. They include corpus callosotomies and multiple subpial transactions.

IS SURGERY EFFECTIVE?

There is very compelling evidence that a temporal lobectomy is an effective procedure, while there is reasonable evidence of the effectiveness of various other surgical procedures for epilepsy. A randomised controlled trial demonstrated that 58% of patients presenting to a tertiary care epilepsy service with medically refractory temporal lobe seizures were free of seizures that impaired awareness 1 year after a temporal lobectomy, while only 8% of patients continuing on medical therapy were free from seizures with loss of awareness after 1 year. The study findings indicate that, compared with continuing medical therapy, one needs to operate on about 2 patients with refractory temporal lobe epilepsy to render 1 patient free from seizures with loss of awareness, and about 3 patients to render 1 patient free of all seizures, including auras.

One may indirectly contrast this with the results of the randomised controlled trials of levetiracetam and vagal nerve stimulation as add-on therapy for medically refractory epilepsy. Compared with placebo, about 7 patients need to be treated with 1 000 mg levetiracetam daily for 1 patient to experience a 50% reduction in seizures at about 3 months. Compared with 'low-intensity' stimulation, about 8 patients need to have vagal nerve stimulators implanted and set to 'high-intensity' for 1 patient to have a 50% reduction in seizures at about 3 months. In the latter studies the outcome measures are much more lenient and the follow-up is shorter than the RCT of temporal lobectomies.

In the above-mentioned randomised controlled trial of temporal lobectomy, patients had a better quality of life and were more likely to be working or to be at school 1 year after surgery than those continuing with medical therapy. A report of a cohort of 79 patients followed up for 10 years after temporal lobectomy demonstrates that its benefits are sustained. There is some evidence that temporal lobectomy may reduce but not normalise the excess mortality associated with epilepsy. Using available data and modelling, economic evaluations assessing the costs and consequences of surgery for patients with medically refractory temporal lobe epilepsy suggest that surgery is likely to be more effective than continued medical therapy and cheaper in the medium and long term.

There are a plethora of case series reporting the efficacy of various neocortical resections, generally reporting seizure-free rates of between 30% and 50%. A corpus callosotomy appears to produce worthwhile improvement in about half of patients. It is most often performed for drop attacks (e.g. in Lennox-Gastaut syndrome).

The quality of the pre-surgical evaluation and surgery may influence both the efficacy and rate of adverse effects but there are as yet no data concerning this issue.

IS SURGERY NOT RISKY?

As the goal of surgery is to improve quality of life, it should not be attempted unless the potential benefits outweigh the potential risks considerably. Apart from the small anaesthetic risk, general risks of neurosurgery include a very low risk of strokes and infections. Other risks have to be individually determined, depending upon the region of cortex to be resected. In a randomised controlled trial of temporal lobectomy, a clinically important change in memory was observed in about 5% of patients. Varying degrees of word-finding difficulties occur after dominant temporal resections, depending on the extent of surgery. Contralateral, peripheral, superior quadrant visual field dysfunction after temporal lobectomy is usually asymptomatic.

SUMMARY

A patient with epilepsy wants to be seizure free. To achieve this, the treating doctor should attempt to define the aetiology or syndrome as this has prognostic and therapeutic implications. Understanding the patient's quality of life and values/preferences may influence therapeutic decisions. While medication remains the first therapeutic option for a patient with seizures, patients with medically refractory seizures need to be identified as early as possible if a plethora of long-term consequences of epilepsy are to be avoided.

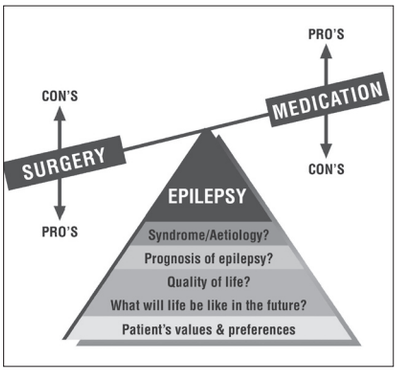

Fig. 2. A suggested framework for assessing patients with refractory epilepsy.

The possibility of epilepsy surgery then needs to be explored, with a careful understanding of how the potential benefits and disadvantages may influence an individual's future life and how this compares with the advantages and disadvantages of continued medical therapy (Fig. 2).

Patients often find the prospect of surgery daunting. They commonly reject the idea initially, then gradually become informed about the relevant issues, and then feel that surgery cannot be performed soon enough! Patients typically need support systems during the process of education, pre-surgical evaluation, surgery and recovery. Education should include realistic goals. Ultimately the experience is a happy one for many patients, with substantial benefits for their quality of life and their future. It appears to avert costs to society.

Further reading

Behrens E, Schramm J, Zentner J, Konig R. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. *Neurosurgery* 1997; **41**: 1-9.

Cockerell OC, Johnson AL, Sander JW, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. *Epilepsia* 1997; **38**: 31-46.

Engel JJ. Surgery for seizures. *N Engl J Med* 1996; **334**: 647-652.

Foldvary N, Nashold B, Mascha E,*et al*. Seizure outcome after temporal lobectomy for temporal lobe epilepsy: a Kaplan-Meier survival analysis. *Neurology* 2000; **54**: 630-634.

Holmes LB, Harvey EA, Coull BA, *et al*. The teratogenicity of anticonvulsant drugs. *N Engl J Med* 2001; **344**: 1132-1138.

Kellett MW, Smith DF, Baker GA, Chadwick DW. Quality of life after epilepsy surgery. *J Neurol Neurosurg Psychiatry* 1997; **63**: 52-58.

Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000; **342**: 314-319.

Lendt M, Helmstaedter C, Kuczaty S, Schramm J, Elger CE. Behavioural disorders in children with epilepsy: early improvement after surgery. *J Neurol Neurosurg Psychiatry* 2000; **69**:739-744.

Sillanpaa M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. *N Engl J Med* 1998; **338**: 1715-1722.

Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001; **345**: 311-318.

IN A NUTSHELL

The epilepsies are common.

Approximately 70% of patients will attain freedom from seizures for at least 5 years.

Those destined to remit usually do so in the first few years after presentation.

The anti-epileptic drugs (AEDs) do not alter the course of epilepsy and are therefore symptomatic treatment only.

For patients with focal epilepsy with or without secondary generalisation, there are no clear differences in efficacy between all of the AEDs, except ethosuximide (used only for absence seizures).

The newer generation AEDs have not reduced the burden of patients with medically refractory seizures.

Medically refractory seizures usually impair quality of life substantially, increase mortality and result in considerable direct and indirect costs to society.

Early referral of patients with medically refractory seizures is required if patients with non-epileptic seizures are to be identified to prevent unnecessary, prolonged treatment with AEDs and if patients with epilepsy are to gain the most from epilepsy surgery.

Epilepsy surgery is an effective treatment option for some patients who have medically refractory epilepsy.

Surgery is usually offered when risks of the procedure are low.