College Lecture†

Medically refractory epilepsy

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Summary

The majority of patients with epilepsy achieve optimal seizure control with rational drug therapy. Either epilepsy surgery or vagus nerve stimulation could help those who are refractory to medical treatment. Potential candidates for epilepsy surgery need to go through an extensive protocol of presurgical evaluation. The appropriate surgical approach is decided upon the outcome of this evaluation. Vagus nerve stimulation is an option for those who are not optimal candidates for surgery.

Introduction

The prevalence of epilepsy is around 5-10 per 1000 and the incidence is 1/2000/year in the population according to epidemiological data from the west[1]. About 80% of patients achieve complete or optimal seizure control with monotherapy. In those who fail to respond there is a 10-15% chance of duotherapy controlling seizures[2]. Occasional patients achieve their best possible control on three antiepileptic drugs. However polytherapy is associated with certain risks such as increased teratogenicity and adverse effects. Despite optimal drug therapy about 10-20% of patients continue to have seizures. They constitute a category identified as 'medically refractory epilepsy'.

Medically refractory epilepsy

This could be defined as 'epilepsy where acceptable seizure control can not be achieved, despite adequate trials with the potentially effective drugs, alone or in combination, at doses or levels that are associated with no side effects or acceptable side effects only'[3]. The concepts included in this definition can not be described in absolute terms. What constitutes acceptable seizure control varies among different individuals. It depends on seizure characteristics as well as the degree of acceptability of the condition to the patient. It is generally accepted that at least 2 or 3 trials with monotherapy and one with combined therapy should be attempted before labeling one as refractory to drugs. The issue of 'acceptable side effects' is also by and large an individual matter, which includes both idiosyncratic and dose related side effects.

Management

If seizures are not under control, it is of utmost importance to review the history and drug therapy carefully. Those who are genuinely refractory to antiepileptic medication need detailed evaluation to ascertain their suitability for potentially beneficial treatment strategies; epilepsy surgery and vagus nerve stimulation.

Epilepsy surgery

The modern era of epilepsy surgery began way back in 1886[4]. It has further revolutionised with the advent of MRI and functional imaging. Surgical intervention can radically change the prognosis of refractory epilepsy. Those who suffer from medically refractory partial epilepsy with no contraindications to surgery are the potential candidates[5] (Table1). They need to go through an extensive protocol of presurgical evaluation (Table 2). The aims of such an evaluation are to establish refractoriness, to localise the epileptogenic lesion, to select the optimal surgery approach and to evaluate the risk: benefit ratio.

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Table 1

Candidacy for epilepsy surgery

1. Medically refractory partial seizures - simple and/or complex and or secondary generalised
   a) at least 2 complex partial seizures per month or less frequent but more severe seizures
   b) duration > 2-3 years
   c) at least four drugs tried
2. Stereotyped onset - favourable factor as it indicates seizure origin from a single focus
3. The occurrence of frequent secondarily generalised seizures and multiple seizure types are adverse prognostic factors
4. No contraindications e.g.
   a) minor seizures that do not impair the quality of life
   b) repeated non epileptic attacks
   c) age> 40 y
   d) chronic psychosis (but not peri-ictal psychosis)
   e) extensive intellectual deficits
   f) widespread lesions or disease
   g) progressive neurological disease
   h) unfit for prolonged anaesthesia

(NB. All these contraindications are relative)

Table 2
Presurgical evaluation

1. Clinical
   History and examination
2. EEG
   a) Non invasive - interictal, video-telemetry
   b) Semiinvasive - foramen ovale electrodes
   c) Invasive - intracranial electrodes
3. Neuroimaging
   a) Structural - MRI
   b) Function - PET, SPECT, functional MRI, MR spectroscopy
4. WADA Test
   For language and memory localisation
5. Neuropsychology
6. Neuropsychiatry
7. Presurgical counselling

Types of surgery

The epileptogenic lesion should either be resected out or disconnected preventing seizure propagation, to surgically treat epilepsy. Based on this principle there are three broad categories of surgical approaches; focal resections, lobar/ multilabor resections and functional procedures to interrupt seizure spreading pathways.

Focal resections

Focal resection should be considered when seizures are caused by a well-localised and isolated lesion. Such abnormal foci are either foreign tissue lesions or hippocampal sclerosis. Low grade gliomas, dysembryoplastic neuroepithelial tumours, vascular malformations, post-traumatic scars and cortical dysplasia are commonly found foreign tissue lesions at surgery. Refractory temporal lobe epilepsy may be due to underlying hippocampal sclerosis which can develop following febrile convulsions in childhood.

Lobar and multilobar resections

These are more extensive forms of surgical resection. Temporal lobectomy is indicated when the epileptogenic lesion is widespread within the temporal lobe. Extratemporal lesions are often located in close proximity to eloquent areas of the brain. Cortical mapping is required prior to surgery in such patients, using functional MRI or invasive EEG. Severe unilateral hemisphere damage as in infantile hemiplegia and large congenital malformation of one hemisphere may result in refractory epilepsy. Such cases with severe fixed neurolpogical deficits are suitable candidates for hemispherectomy as a form of surgical therapy. The speech dominant hemisphere could be safely resected in children under 8 years as language functions can subsequently develop in the other hemisphere after surgery. However this is less likely to occur in older age groups, restricting the operation to the non-dominant hemisphere[5]. Anatomical hemispherectomy carries the risk of cerebral haemosiderosis and obstructive hydrocephalus as long term complications. Several modifications of the procedure have been described to overcome this problem.

Interruption of seizure pathways: Callosotomy

In certain patients, rapid spread of seizure activity from one hemisphere to the other via corpus callosum results in very sudden drop attacks. Sectioning the corpus callosum (callosotomy) is essentially a palliative procedure in such cases where the seizure focus can not be identified. This operation is aimed at reducing the severity of drop attacks and resulting injuries. Other indications for callosotomy are less well defined, which include generalised tonic clonic seizures, complex partial seizures of multifocal origin with capacity for secondary generalisation and secondary generalised seizures where the focus can not be localised.

Interruption of seizure pathway: Multiple subpial transection

Multiple subpial transection is recommended for patients with epileptogenic zones involving eloquent brain cortex where resection is not feasible due to the risk of serious post operative neurological deficits[8]. In this operation multiple incisions are made throughout the epileptogenic zone which would prevent seizure propagation in the horizontal plane while preserving important afferent and efferent pathways arranged vertically.

Outcome of surgery

The benefits of surgery include seizure control as well as improvement in psychosocial functioning. In some patients seizure control may not be immediate but takes place gradually over several months. The outcome depends on many variables such as the site of resection, whether a focal pathology is removed or not, and the nature/ extent of the focal pathology.

Generally the outcome in temporal lobe surgery tend to be better than in extratemporal. The best outcome is seen following resection of low grade gliomas, dysembryoplastic neuro-epithelial tumours, and smallcryptic vascular malformations where 70-80% of cases become seizure free[8]. Around 60% of patients are rendered seizure free following temporal lobe surgery for

hippocampal sclerosis[10]. Large and complex vascular malformations are less favourable for surgery with less than 60% becoming seizure free. Cortical dysplasia is the least responsive pathological condition for epilepsy surgery. If no pathology is removed only less than 20% are rendered seizure free[5]. Complete control or marked reduction of seizure tendency is achieved in 86% of patients after hemispherectomy[11].

The risks of surgery include general complications such as haemorrhage and infection, neuropsychological deficits, psychiaric morbidity and neurological deficits. A variety of neurological deficits have been reported depending on the site and extent of surgery. Hemiplegia, visual field defects and language/memory impairment could occur following temporal lobe surgery and the risk of a major deficit is about 1%. Frontal lobectomy is associated with a 3% risk of hemiparesis[5]. Chronic ongoing epilepsy itself carries a risk of sudden unexpected death in the order of 1/200/year,[13] which should be borne in mind when assessing the risks of surgery.

Vagus nerve stimulation (VNS)

Electrical stimulation of the vagus nerve has been found to produce significant anticonvulsant effects in experimental models, in pilot studies in humans and subsequently in double blinded randomised trials[13,14]. The device of VNS consists of a pacemaker like stimulator, which is implanted subcutaneously and bipolar stimulating electrodes wrapped around the left vagus nerve in the carotid sheath. Trains of electrical pulses generated in the stimulator are delivered to the nerve via electrodes. The left vagus nerve is selected as the majority of cardiac efferents to the atrio-ventricular node run via the right vagus.

At present VNS is recommended for patients with medically refractory partial epilepsy who are not optimal candidates for surgery[13,14]. The mode of action of this device is not well understood. However PET studies have shown increased blood flow to several regions of the brain including the thalamus and cerebellum during stimulation[15]. It might probably indicate that these regions play some role in modulating the seizure activity.

There is evidence that VNS produces a reduction in seizure frequency as well as in seizure severity[16]. High stimulation has been shown to be more effective than low stimulation. With high stimulation the mean reduction in seizure frequency is about 25-30%[13,14]. Common side effects of this technique are hoarseness, throat pain and cough during stimulation[13,17].

Chronic cerebellar stimulation and stimulation of the centromedian nucleus of the thalamus have also demonstrated anticonvulsant effects in humans. However these methods have not yet come into wide clinical practice.

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