Refractory Epilepsy

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Abstract

Refractory Epilepsy (R.E.) is a condition where all antiepileptic drugs (AEDs) fail to provide adequate seizure control. To diagnose R.E., false cases of refractoriness need to be carefully excluded. There are several predictors of refractoriness. The treatment options in R.E. are resective surgery, ketogenic diet and vagal nerve stimulation. The roles of newer AEDs are also promising. The future therapeutic possibilities include deep brain stimulation, AED containing polymers, stem cells and gene therapy.

Introduction

Up until the late 60s it was widely believed that a vast majority of the people of epilepsy had a refractory disorder. But with the advent of a wide range of anti-epileptic drugs (AED) particularly over the past two decades and development of technology, considerable number of previously untreatable cases of epilepsy can now be successfully brought under control as well as underlying cause can be ascertained. In 2000, Kwan and Brodie in their landmark report stated that with single AED around 47% of the newly-diagnosed epilepsy can be made seizure-free. A further 13% of patients can be controlled on their 2nd AED. With 3rd AED or with combination of AEDs a further 4% undergo remission. But the remaining 30-35% of the epileptic disorders cannot be made completely seizure-free with medical treatment. The International League Against Epilepsy (ILAE) task force recently defined “Drug-resistant Epilepsy” as failure of adequate trials of two tolerated, appropriately chosen and used AED schedules as monotherapy or in combination to achieve sustained seizure freedom. This is a slightly different condition from “Refractory (or Intractable) Epilepsy (R.E.)”. R.E. is defined as a condition of epilepsy where all drug choices used singly or in combination have failed to provide adequate control of seizure.

Symptomatic epilepsy particularly complex partial or secondarily generalized tonic-clonic and epilepsy in persons with neurological deficit have the propensity to be R.E. In neonates and children, a wide range of epilepsy syndromes that constitute “Epileptic Encephalopathy” manifest as R.E. These epilepsy syndromes are listed in Table 1.

Predictors of R.E.: Clinical determinants for predicting future refractoriness are (A) Epilepsy syndromes, (B) response to initial 2 AEDs, (C) seizure frequency at epilepsy onset, (D) age, (E) inter-ictal spike discharges and (F) co-morbid depressive illness.

Table 1: Refractory Epilepsy in infants and children

- Ohtahara syndrome
- Early myoclonic encephalopathy
- West syndrome
- Dravet’s syndrome
- Lennox-Gastaut syndrome
- Epilepsy with continuous spike-wave in slow wave sleep ± Landau-Kleffner syndrome
- Myoclonic status in non-progressive encephalopathy
- Hypothalamic gelastic epilepsy

A. Epilepsy syndromes as listed in Table 1 are the typical examples of R.E. Among the focal epilepsy cases, R.E. is common in hippocampal sclerosis, cortical dysplasia and cortical hemorrhage. The site of epileptogenic zone also is a predictive factor. Temporal lobe is the most epileptogenic area as ‘kindling’ can easily be elicited by stimulation of amygdala.

B. Absence of seizure freedom when 2 appropriate AEDs proved inefficient is a crucial predictor of refractoriness. Chance for seizure freedom decreases proportionately as the number of ineffective AEDs increases. Failure after 6 AEDs indicates absolute R.E. (0% seizure freedom).

C. High seizure frequency (> 1 seizure per month) occurring soon after the diagnosis of epilepsy correlates with refractoriness both in the short term (2-4 years) and in the long term (30-35 years).

D. Younger age at onset of epilepsy is a predictive factor for R.E.. Epileptic seizures occurring in immature brain results in non-pruning of neurons and contribute to the existence of a high number of gap junction communications. This ultimately leads to abnormal neural connectivity in brain, termed as “hyper-connected cortex”, the precursor of R.E.

E. There is some association of R.E. with the number of spike discharges as well as with the presence of multi-focal spikes in inter-ictal EEG.

F. Co-existent depression is a predictor of R.E. Neurobiological processes that underpin depression may interact with those producing seizure and increase the likelihood of development R.E.

What is the necessity for early identification of R.E.? Uncontrolled seizures have devastating impact on social functioning and may even lead to psychiatric complications. There is also a heightened risk of mortality due to seizure-related accidents or due to SUDEP (sudden unexpected death associated with epilepsy). Recurrent seizures have long-term adverse effects on cognition and behavior. Early intervention may prevent or minimize the risks of all these complications.

Diagnosis of R.E.: At the outset it is very important to exclude cases of “pseudo- refractory epilepsy” that include the various non-epileptic paroxysmal events, as listed in Table 2. Factors that lower seizure threshold (Table 3) also may present as false R.E. Last but not the least, non-compliance of AED is an important factor for pseudo-refractoriness. In fact, studies have shown that around 30-50% of patients with epilepsy do not comply with their prescribed AED therapy. Once the cases with false refractoriness have been excluded, and the patients have more than 1 epileptic attack per month for at least a year in spite of appropriate AEDs in adequate dose, the diagnosis of R.E. is
Table 2: Causes of non-epileptic paroxysmal events

- Shuddering attacks in infancy
- Breath-holding spells in infancy
- Benign paroxysmal vertigo in childhood
- Tics and habit spasms
- Paroxysmal choreoathetosis
- Migraine
- Syncope and cardiac arrhythmias
- Hyperventilation syndrome
- Panic attacks
- Transient global amnesia
- Transient ischemic attack
- Acute confusional state
- Psychogenic seizures

Table 3: Factors lowering seizure threshold

- Sleep deprivation
- Alcohol or barbiturate withdrawal
- Dehydration
- Drug interaction-quinolone and carbapenem antibiotics, antihistaminics, phenothiazines, tricyclic antidepressants, etc.
- Systemic infections
- Malnutrition
- Trauma
- Hyperventilation
- TV screen malfunction, flashing lights
- Gastro-intestinal upset

established. These R.E. candidates need to be evaluated in a specialized center for further diagnostic tests, optimization of pharmacotherapy and for consideration of alternative treatments which include surgery.

Surgical treatment of R.E. Once the diagnosis of R.E. is established, the possibility of Resective Surgery to cure or at least adequately control seizures should be explored. The ideal surgical candidates have (i) well-circumscribed MRI lesions, (ii) well-localized inter-ictal discharge, (iii) clinical feature indicative of focal-onset of seizure, (iv) concordance of nos. 2 and 3 findings, (v) low risk of deficit after surgical resection of focus, and (vi) absence of other potentially epileptogenic focus. Temporal lobe lesions, namely, mesial temporal sclerosis, cavernous angioma or low grade tumor have 94% chance of excellent seizure control post-operatively. On the other hand, frontal lobe lesions have post-operative 72% chance of excellent seizure control. These cases should undergo epilepsy surgery evaluation soon after the seizure fails to be controlled with 2nd appropriate AED. Although the number of post-operative seizure-free state diminishes to some extent over the years, still this case could be better managed with AEDs than those who did not undergo surgery. The best outcome after resective surgery is in mesial temporal sclerosis. Surgery is also indicated in cases of non-lesional extra temporal epilepsy, multiple lesions like multiple cavernous angioma or tubers, bilateral hippocampal atrophy, epileptogenic focus at eloquent cortex, large multi-lobar lesions and in some cases of epileptic spasms and atonic seizures. To localize accurately epileptogenic focus in these latter cases, many sophisticated invasive and non-invasive investigations are now available (Table 4). Concordance of the different diagnostic modalities helps to accurately localize the seizure focus for temporal/extra-temporal lobectomy or lesionectomy. Computer-image guided navigational surgery is the latest surgical technique introduced to excise the focus with precision. Apart from resective surgery of epileptogenic lesions, there are other surgical approaches used in R.E. These are

- Hemispherectomy: for temporo-parietal resection in Kozhevnikov-Rasmussen syndrome
- Corpus Callosotomy: where anterior 2/3rd of corpus callosum is excised to minimize risk of fall and injury, as in intractable drop attacks from atonic, tonic-clonic or tonic seizures.
- Multiple Subpial Transections: a series of shallow cuts 1/4th inch deep around epileptic focus, when the focus could not be completely resected due to the presence of important cortical function.

Other treatment modalities: This includes ketogenic diet and vagal nerve stimulation.

**Ketogenic diet**: This high fat, low carbohydrate diet reduces seizures in children with various focal or generalized R.E.. This diet is particularly effective in Doose, Dravet’s, tuberose sclerosis, etc. This also leads to behavioral improvement. Improvement of seizure frequency starts within 2 weeks. About 40% has at least 50% reduction in seizure frequency and 5% actually becomes seizure free. But 10% has side-effects like hypoproteinemia, weight loss, growth failure or renal stones. Fifty percent of subjects have been found to discontinue therapy after 1 year mainly because of unpalatable taste of the diet.

**Vagal nerve stimulation (VNS):** VNS is an implantable device approved for those cases of R.E. who are above 12 years of age. This is useful in diverse seizure semiology -focal, generalized, tonic, atonic or infantile spasms. The device includes a chest pacemaker with electrode in left cervical vagal nerve. The possible complications include vocal cord palsy (1%), infection (1%), cough, diminished figural memory, Horner’s syndrome and neck pain. On the average about one-third have 50% reduction of seizures. However, seizure freedom rarely occurs.

**Role of newer AEDs.** Some authors do not believe that refractoriness or intractability of epilepsy is inevitable if seizure control is not achieved within the first few years of medical treatment. According to them, with the introduction of new AEDs (levetiracetam, lamotrigine, topiramate, zonisamide, lacosamide, rufinamide, stiripentol, etc.) there has been improved seizure control in a substantial number of cases. They demonstrated that addition of new AED provides seizure freedom in 17% and a 50-99% seizure reduction in about 28%. Levetiracetam is one of the newer AED which is now widely used in the treatment of epilepsy, both in adults and in children. It is a broad spectrum AED with demonstrated significant efficacy as add-on therapy in idiopathic generalized as well as in focal onset refractory seizure, but more effective in the latter group. “Rational polytherapy” (combining AEDs of
different mechanisms of action) should be considered, because that may have synergistic effect and also a less adverse reaction. For example, the combination of lamotrigine and valproate is found to be very effective for partial seizures. There are a number of newer AEDs currently under investigation, i.e., retigabine (potassium channel opener), perampanel (AMPA receptor antagonist), ganaxolone (GABA_A receptor agonist), brivacacetam (SVA-2 ligand antagonist) and so on. So the future of pharmacotherapy in R.E. seems to be promising.

Temporal pattern of refractoriness in epilepsy: It is believed that in most cases pharmacoresistance is constitutive and hence fully developed before the first seizure or at least before the start of AED. But there are now evidences to show that some patients with initially easily treatable seizures developed R.E. years later. Another hypothesis claims that drug resistance may remit and reappear in the course of the disease. But this latter theory is controversial since the temporary remission could be the result of the addition of new AED.

Mechanism underlying refractoriness in epilepsy: Two major hypotheses exist, i.e., (A) Target hypothesis, and (B) Transporter hypothesis. According to target hypothesis, there is alteration of the receptor (which binds to the AED) at the neuronal target site, thereby reducing overall drug efficacy. On the other hand, according to transporter hypothesis there is enhancement of blood-brain barrier (BBB) efflux transport, thereby reducing the penetration of AED across BBB to reach the epileptic neurons.

Therapeutic possibilities of the future: The future therapeutic possibilities for treatment of R.E. are immense. To suppress epileptic seizure, deep brain stimulation at anterior thalamus or at centromedial nucleus is under investigation. A cranially implanted responsive neurostimulator that detect EEG activity of seizure and then trigger delivery of electric pulse to the focus to terminate seizure is being devised. Apart from this, research is under way to create 2-3 mm microspheres containing ‘polymers’ with AED in it. This micropolymer might be implanted near the cerebral epileptogenic zone. The advantage of this micropolymer apart from increased efficacy is that it eliminates the possibility of non-compliance and also bypasses the blood-brain barrier. Hopefully, the future device may be able to predict seizures also and at the same time automatically administer AEDs to prevent occurrence of seizure. Cell transplantation and gene therapy hold great promise but their clinical application will perhaps be in distant future.

References