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REVIEW

Managing drug-resistant epilepsy: challenges and solutions

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Abstract: Despite the development of new antiepileptic drugs (AEDs), ~20%–30% of people with epilepsy remain refractory to treatment and are said to have drug-resistant epilepsy (DRE). This multifaceted condition comprises intractable seizures, neurobiochemical changes, cognitive decline, and psychosocial dysfunction. An ongoing challenge to both researchers and clinicians alike, DRE management is complicated by the heterogeneity among this patient group. The underlying mechanism of DRE is not completely understood. Many hypotheses exist, and relate to both the intrinsic characteristics of the particular epilepsy (associated syndrome/lesion, initial response to AED, and the number and type of seizures prior to diagnosis) and other pharmacological mechanisms of resistance. The four current hypotheses behind pharmacological resistance are the "transporter", "target", "network", and "intrinsic severity" hypotheses, and these are reviewed in this paper. Of equal challenge is managing patients with DRE, and this requires a multidisciplinary approach, involving physicians, surgeons, psychiatrists, neuropsychologists, pharmacists, dietitians, and specialist nurses. Attention to comorbid psychiatric and other diseases is paramount, given the higher prevalence in this cohort and associated poorer health outcomes. Treatment options need to consider the economic burden to the patient and the likelihood of AED compliance and tolerability. Most importantly, higher mortality rates, due to comorbidities, suicide, and sudden death, emphasize the importance of seizure control in reducing this risk. Overall, resective surgery offers the best rates of seizure control. It is not an option for all patients, and there is often a significant delay in referring to epilepsy surgery centers. Optimization of AEDs, identification and treatment of comorbidities, patient education to promote adherence to treatment, and avoidance of triggers should be periodically performed until further insights regarding causative pathology can guide better therapies.

Keywords: drug-resistant epilepsy, pharmacoresistant, management, review

Introduction

Epilepsy is one of the commonest neurological conditions,[1] with an estimated prevalence of 0.5%–1%.[2] Patients with epilepsy who have seizures that do not successfully respond to antiepileptic drug (AED) therapy are considered to have drug-resistant epilepsy (DRE). The definition for DRE varies, but generally, two appropriate and tolerated AED schedules, whether as monotherapies or in combination, must have been trialed before this term can be applied.[3] The condition has also been referred to as intractable, pharmacoresistant, or medically intractable epilepsy; however, intractable seizures are merely one manifestation of DRE. Equally as relevant are the neurobiochemical changes, cognitive decline, and psychosocial dysfunction comprising important components in this multifaceted condition.[4]

Significant interindividual variation among patients with DRE poses a challenge to researchers and clinicians alike. For example, some epilepsy patients have multiple

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seizures per day, reduced to one per day with treatment. Other individuals have one seizure per month, reduced to years between seizures with appropriate therapy. In both cases, AED treatment reduces seizure frequency but does not completely stop the individual from having seizures. Therefore, should a diagnosis of DRE be made? Similarly, the severity of seizures is less commonly considered in the definition of DRE.[5] Confounding this are external factors that can contribute to a misdiagnosis of DRE and subsequent mismanagement. Seizures in the setting of sleep deprivation, intercurrent illness, or menstruation should not prompt an immediate change of an AED, and all attempts to exclude mimics, such as psychogenic non-epileptic seizures (PNESs), should be made.

The heterogeneity among DRE patients makes comparison of trials and defining practice guidelines fraught with difficulty; thus, a precise definition of what constitutes DRE remains elusive. A more recent proposal by the International League Against Epilepsy has lessened the ambiguity around diagnosing DRE. For an AED to be deemed effective, there should be a seizure-free period of a minimum of three times the longest pretreatment inter-seizure interval, or 12 months, whichever is longer.[3] Additionally, the AED or intervention trialed to help achieve a seizure reduction must be applied for an adequate period of time, be selected appropriately for the individual's seizure or epilepsy type, and be prescribed at a sufficient dose. There are no standardized parameters for what period of time is "adequate", but generally, it is accepted that a minimum of 6 months is necessary.[6] Nor is there a clinically effective dose range available for every AED, as this varies depending on multiple factors affecting drug clearance. Complicating this is the issue of medication tolerability and the adverse side effects that patients with epilepsy and DRE experience, placing further limitations on management.[7] Finally, despite many advocating for early referrals to epilepsy surgery centers, a significant delay exists.[8]

With these difficulties in mind, it is clear that patients with DRE represent a diverse group with a dichotomy of management challenges that should address the pharmacological, psychological, and social issues that are part of this condition.

Challenges

The exact incidence and prevalence of DRE are uncertain, due to the varied definitions, as well as misdiagnosis. Despite adequate treatment and adherence, and the emergence of newer AEDs, over 30% of patients with epilepsy will continue to have seizures.[9,10] This number is expected to rise with the aging population,[11] although generally, seizures in those with new-onset epilepsy in the elderly tend to be more easily controlled.[12] Conversely, there are patients meeting the criteria for DRE who do proceed to achieve prolonged ($\geq$12 months) periods of seizure remission. However, the risk of seizure relapse in these individuals is high, with a >70% noted in one series.[13] The challenge lies in managing these often complicated patients, with adverse drug effects limiting the use of some AEDs, and the wider need to address the burden of epilepsy-related disabilities.

Predictors

Identifying those individuals who are most at risk of seizure relapse and development of DRE remains a challenge. A number of prospective studies have attempted to identify factors that may predict DRE development. These have varied in their sampling and whether they included children, adults, or both. Regardless of the groups studied, it is accepted that the basis for this "refractoriness" is likely to be multifactorial. To date, features identified include those relating to the "intrinsic" factors of the underlying epilepsy (eg, type of epileptic syndrome, presence of structural abnormality), an individual's response to his/her first AED, and a high number of seizures prior to diagnosis and treatment.

"Intrinsic" factors

In general, evaluation of the patient should take into account any idiopathic syndromes as well as causative neuropathology.[4] For example, certain pediatric epilepsy syndromes, including Lennox–Gastaut syndrome, Rasmussen encephalitis, and early infantile epileptic encephalopathy among others, are almost invariably drug refractory. Similarly, underlying structural abnormalities in non-idiopathic localization-related epilepsies, which account for >50% of adult cases of DRE, must be considered.[14] A common observation is that epilepsy from an underlying vascular lesion is more treatment responsive than that due to mesial temporal sclerosis (MTS), cortical dysplasia, or dual pathology.[15,16] In fact, it has been observed that up to 80% of individuals with MTS develop DRE[15] and these individuals are unlikely to benefit from ongoing medication trials alone.

AED response

The response an individual has to his/her first AED has been shown to be a powerful prognostic indicator of the development of DRE.[4,17] Kwan and Brodie reviewed 525 patients with newly diagnosed epilepsy of all types.[9] While more than half of the patients responded to the first AED

prescribed, <20% responded to subsequent drug trials. Of the patients with a suboptimal response to their first AED, 41%–55% became seizure free if treatment failure was due to poor drug tolerability or idiosyncratic reactions, compared with only 11% of patients who failed their first AED due to the drug being ineffective. This demonstrates that the likelihood of successful treatment with other drugs diminishes with each AED failure, suggesting that treatment resistance can be predicted early on.

Other factors predicting response

Another consistently identified risk factor for DRE is having a high number of seizures prior to diagnosis and treatment.[9] More variably associated negative predictors for seizure remission include a presentation with status epilepticus, a family history of epilepsy, a history of febrile convulsions, and an abnormal electroencephalogram (EEG). It has also been suggested that age at presentation may be a factor in DRE development. In at least one series, onset of seizures in the neonatal time period has been associated with DRE.[18] Similarly, those who develop epilepsy later in life (>65 years) appear less likely to develop DRE, possibly relating to the underlying pathogenesis that also varies with age.[19]

Predicting those patients unlikely to respond to medical treatment allows attention to be focused on other interventions such as epilepsy surgery. Early identification of these individuals is favorable, but not always possible, with cases of DRE emerging after years of excellent seizure control. The next challenge is to determine whether medical intractability is a feature of epilepsy at the time of presentation, or whether it evolves over time.

Pathogenesis

Management of patients with DRE is challenging because the mechanism underlying it is not completely understood nor do we understand why pharmacoresistance develops in some individuals and not others. The pathogenesis underlying DRE is likely to be multifactorial and variable with both genetic and environmental factors implicated[4,20] and several theories for how DRE develops.

The "transporter hypothesis" is based on findings of overexpression of multidrug efflux genes and concomitant proteins in human epileptic brain tissue and in animal models of DRE.[21,22] The ATP-dependent transport protein, P-glycoprotein (P-gp), is one of these proteins found to be overexpressed in the blood–brain barrier. Normally, P-gp exports drugs out of cells, helping to protect normal and tumor cells against the influx of xenobiotics.[23] While few epilepsy drugs have been shown to be transported by P-gp, several AEDs have similar chemical structures to P-gp substrates. It is proposed that increased expression and activity of P-gp as an efflux pump limits AED access to the seizure focus, thus conferring the multidrug resistance phenotype. Other efflux transporters in the brain have been implicated in DRE pathogenesis but are less well characterized[24] and differ from P-gp in their substrate specificity, distribution, and structure.[25,26] Studies to detect their presence in the blood–brain barrier have yielded conflicting results, and the extent that these transporters contribute to drug resistance is still relatively unknown. Similarly, whether the overexpression of these efflux transporters is constitutive due to gene polymorphisms, or acquired as a consequence of uncontrolled seizures or chronic AED treatment, remains unresolved. Current preliminary evidence suggests that both could be occurring.[26]

In contrast, the alternative "target hypothesis" suggests an epilepsy-induced alteration of cellular targets of AEDs, leading to a reduction in sensitivity. These targets include various receptors and ion channels, but this hypothesis is principally based on studies with carbamazepine (CBZ) on voltage-gated sodium channels in hippocampal neurons.[27] Sodium channels of hippocampal CA1 neurons from patients with MTS were studied and compared with neocortical neurons from patients without MTS. The mechanism of action of CBZ, use-dependent block of voltage-dependent sodium channels, was completely lost in these DRE patients. Similarly, a loss of drug-target sensitivity has also been found in rat models of temporal lobe epilepsy.[28] What remains to be determined is whether the loss of sodium channel sensitivity with CBZ in patients with DRE extends to other AEDs. Subsequent studies attempting to address this found that other AEDs with a similar mechanism of action, such as valproate (VPA) and lamotrigine (LTG), did not display a loss or marked reduction in sodium channel sensitivity.[29] Other targets, such as $GABA_A$ receptors and their alterations in epilepsy, provide some further support for this hypothesis but are in no way conclusive.[30,31]

Other hypotheses have emerged more recently, born from findings in patients and animal models of DRE. The "network hypothesis" proposes that seizure-induced structural brain alterations such as axonal sprouting, synaptic reorganization, neurogenesis, and gliosis can contribute to the formation of an abnormal neural network. This network avoids the inhibitory effect of an endogenous antiepileptic system and prevents AEDs from entering their targets, eventually leading to DRE. This is supported by the clinical finding of surgical

resection of an altered network counteracting AED resistance and leading to seizure reduction.[32] The "gene variant hypothesis" suggests that there is an inherent resistance that is governed by genetic variants of proteins that are involved in the pharmacokinetics and pharmacodynamics of AED activity. Finally, the "intrinsic severity hypothesis" suggests that an increased disease severity leads to drug intractability.[33]

What is more realistic is to consider that DRE is not caused by a single mechanism but is instead due to several mechanisms, which may even occur in the same patient.[34] As has occurred in oncology, studying the basis of DRE is important to predict poor response to AED treatment and hopefully offer new treatment approaches.

Complications

The complications of DRE and its management are well described.[35] There is an increased risk of injuries and premature mortality in those aged <50 years, with varying estimates provided across countries. This can be due to the underlying cause of epilepsy (eg, cerebral neoplasm, neurodegenerative disease), directly seizure related (ie, seizure-related accidents and status epilepticus) or due to sudden unexpected death (SUDEP).[36]

Of note, SUDEP is 40 times more likely in patients with ongoing seizures than in those who are seizure free,[37] and is the most common cause of premature death among individuals with epilepsy.[38] While the precise cause of SUDEP is unknown, consistent risk factors include poor seizure control, frequent generalized tonic–clonic seizures, and long-standing epilepsy.[39]

Substantial work has implicated overlapping cardiac, respiratory, and autonomic domains as a mechanism. It has been postulated that SUDEP starts with an early, centrally mediated, severe alteration of both respiratory and cardiac functions after generalized tonic–clonic seizures.[40] No causative genes for SUDEP have been identified, but there are a variety that have been associated with an increased risk, including those for long QT syndrome and Dravet syndrome.[40] There has also been recent animal experiments suggesting a possible brainstem mechanism involving serotonin and adenosine, with abnormalities of sympathetic innervation.[41]

Deaths such as SUDEP are usually nocturnal, and therefore unwitnessed. Given this and the lack of biomarkers for SUDEP, every attempt to prevent seizures is the only intervention to date.

In addition to AED optimization and educating the patient on avoiding seizure-provoking triggers, there may also be a role for seizure detection devices in this group, although these are imperfect and present an additional challenge of affordability. Devices must have a low false-positive rate to be considered; for example, false-positive alarms that wake the patient during sleep may contribute to a converse aggravation of seizures. Potential therapeutic strategies may include pharmacological modulation of respiratory arrest and implantation of cardiac devices to reduce risk, with further research into these initiatives required.

Comorbidities

Identification and management of comorbidities in epilepsy patients is essential, given approximately two-thirds of premature deaths are attributed to comorbid disease.[42] Diseases such as depression, anxiety, dementia, migraine, cardiovascular disorders, asthma, osteoarthritis, and gastroesophageal reflux disease are more common in people with epilepsy than the general population. It is thought that shared risk factors for these conditions and bidirectional relations explain some of these associations, with others explained by the effects of AEDs.[43] Additionally, pregnant women with epilepsy have increased complications. These include an increased risk of spontaneous miscarriage, antepartum or postpartum hemorrhage, hypertension, induction of labor, cesarean section, preterm birth, and fetal growth restriction.[44]

Neuropsychiatric comorbidities deserve particular attention, as they appear more frequently in patients with epilepsy than in the general population. In children with epilepsy, the most prevalent comorbidities include attention-deficit hyperactivity disorder, mood and anxiety disorders, autism spectrum disorders, and behavioral problems.[45] Conditions such as depression and affective and anxiety disorders are most common in adults, yet they are highly underdiagnosed and undertreated.[46] Stress is consistently cited as a factor that triggers or exacerbates seizures. Moreover, depression and suicide prevalence is four to five times higher among patients with epilepsy when compared with healthy population,[47] with the period after the initial diagnosis the most dangerous. Finally, given that epilepsy is common in people with intellectual disability, and both conditions are associated with psychiatric and behavioral comorbidities, this group has particularly complex care needs. It is worth noting that in patients with epilepsy and intellectual disability, the rates of neuropsychiatric disorders are even higher with more severe types of epilepsy, such as DRE.[48]

The overall relationship between psychiatric disorders and seizures remains poorly understood. There is some evidence that the relationship is bidirectional; that is, the

diagnosis of epilepsy acts as a risk factor for depression, and depression acts as a risk factor for the onset of epilepsy.[43] Chronic stress exposure with epilepsy has also been postulated to have a role in depression development, with feelings of isolation, low self-esteem, and sadness often cited by patients with epilepsy. Other risk factors to consider include a family history of psychiatric illness and iatrogenic causes, such as pharmacological or surgical.

Outcomes

Overall, poorer health outcomes are consistently noted in DRE patients,[49] and preliminary evidence suggests that comorbid conditions such as depression and migraine negatively affect seizure outcome and quality of life.[43] Epilepsy affects patients' independence, psychological health, and emotional adjustment. Psychosocially, even infrequent seizures are associated with lower rates of marriage, poorer academic achievement, dependent behavior, and restricted lifestyle and employment opportunities. Almost all DRE patients cannot drive.

Additionally, there is associated cognitive decline in patients due to a combination of high seizure frequency, prolonged seizures, and episodes of status epilepticus.[46] This neuropsychological dysfunction may not be reversible, even if the seizures become controlled. Childhood-onset epilepsy patients who enter remission have been shown to suffer social and educational disadvantages into adulthood. Similarly, surgical outcome studies have noted that even after successful procedures where DRE is eliminated, these patients do not gain employment, or marry or have children, and remain dependent on family and the welfare system.[50]

A change in the public's awareness and attitudes about epilepsy may significantly affect the burden of the disease by reducing associated stigma.[51] Stigma has been known to predominate particularly in developing countries, and forces people with epilepsy to conceal their disease. However, even in developed countries, knowledge surrounding epilepsy is lacking, which was evidenced by a nation-wide phone survey conducted in Italy in 2010.[52] Of those surveyed, 56.6% knew a person with epilepsy, although less were familiar with the cause; 56.1% thought that epilepsy was a psychological/psychiatric disease, 36.5% a form of insanity, and 4.1% an evil spirit possession. Suggestions for improvement in the condition ranged from enrollment in the military to procreation.

Economic considerations

Epilepsy carries high health care costs for society due to the fact that it is a common clinical condition, affecting all ages and often requires long-term treatment. Costs peak in the first year after diagnosis and then vary depending on disease severity, response to treatment, and presence of comorbidities, with just one comorbidity tripling cost.[51] The highest costs are incurred by surgical candidates initially, who are then superseded by patients with DRE. This is due to more frequent hospital admissions, assessments, medications, and other treatments, such as surgery or electronic devices.

Additionally, direct "out-of-pocket" costs to the patients can be significant and are higher in certain countries due to differences in health care infrastructure. Productivity losses for both patients and carers in more severe forms create a substantial economic burden on households. This is further exacerbated by the fact that patients with epilepsy often have a lower income than the general population. There are also higher rates of unemployment in nonsurgically treated DRE patients compared to surgically treated patients.

Noncompliance with treatment

Management is often complicated by drug tolerability and noncompliance, which can be in association with drug and alcohol abuse. AED intolerance can emerge due to the rapid rate of drug titration or drug–drug interactions, or be specific to the drug side effect profile. Manifestations can be mild to life-threatening, but when side effects occur, they most often lead to noncompliance and/or premature cessation of the AED. Prevention of drug toxicity with reduction in seizures is an established driver of better quality of life than seizure reduction alone,[34] and addressing this issue early and continuously is recommended.

Other reasons for noncompliance vary, with patients citing lack of money to buy AEDs, failure to acknowledge the disease, poor response to treatment, and belief that the treatment is of no use. In a large, multinational survey in 2014, Groenewegen et al noted that better informed patients adhered better to their therapy than those who were less well informed.[53] Poor follow-up and patient forgetfulness were also identified as contributors. These findings are promising as there are multiple practical interventions in the physician–patient relationship that can address some of these issues, including improvement in communication and more frequent reviews.

Solutions

Failure of drug response remains a major limitation in the treatment of epilepsy. Of those diagnosed with DRE, only 5% of patients per year will enter seizure remission as a result of medication changes.[13]

The ideal solution involves a massive expansion of specialist services and a better understanding of what genetic and environmental determinants underlie DRE. In understanding the development of DRE, identifying subgroups, and targeting drug therapies to meet the specific needs of these groups, there is hope that remission rates will improve.

Realistically, with the current state of play, good treatment outcomes are still possible. These depend on the physician's ability to correctly diagnose the epilepsy subtype and choose an effective treatment regimen. Human factors including the wrong diagnosis, drug, or dose cannot be overstated. Early referral to specialist epilepsy centers for a comprehensive evaluation in some patients is paramount. If surgery is not indicated after evaluation, other approaches such as electrical stimulation and diet can be considered.

Evaluation

It is important to accurately differentiate between true and apparent DRE, with the erroneous diagnosis of epilepsy needing to be at least considered in patients not responding to AEDs. Treatment failure can occur independent of intractability, and these circumstances are important to consider to ensure that an appropriate therapy is used. Noncompliance with AEDs, inadequate dosing of AEDs, and lifestyle factors that increase seizure frequency, such as drug and alcohol abuse, and sleep deprivation, all contribute to increased seizure frequency but should not contribute to the definition of DRE.

Diagnostic uncertainty and failure to correctly classify patients can contribute to "pseudorefractoriness", leading to an incorrect diagnosis of DRE. Lack of access to specialist services is partly responsible for this, with one UK study noting that ~55% of adult patients receiving treatment for epilepsy had never received specialist advice.[54] An incorrect diagnosis of a particular epilepsy syndrome can cause apparent refractoriness when an inappropriate drug choice is used. For example, generalized genetic syndromes can go unrecognized and be incorrectly treated with AEDs more suited to treating focal epilepsy. An example of this is when CBZ is used for juvenile myoclonic epilepsy. Accounting for 6%–8% of all epilepsies, juvenile myoclonic epilepsy patients present to pediatric and adult neurologists, and other health practitioners, with typical myoclonic jerks often misinterpreted as focal motor seizures, prompting treatment with CBZ. Smith et al retrospectively assessed the case records of 94 DRE patients, identifying six with unrecognized genetic generalized epilepsy. They all became seizure free with the introduction of VPA.[56]

Various studies have noted that the epilepsy misdiagnosis rate is 20%–26%, and is often due to incomplete history taking and misinterpretation of the EEG.[55] Common conditions mistaken for seizures include syncope, cardiac arrythmias, migraine, and transient ischemic attacks. Another condition that is important to recognize is PNESs, with delays to diagnosis up to 16 years in one series.[56] Identification of these individuals is important to avoid iatrogenic harm and to identify and manage the underlying psychological stressor. Diagnosis and management of PNES patients can be difficult due to the fact that some patients with psychogenic seizures may also have epilepsy.

A false-positive diagnosis of DRE can have severe psychological and socioeconomic consequences for the patient, with unnecessary driving restrictions and employment difficulties encountered. Additionally, there are implications for the community in regard to distribution of health resources and welfare.

Evaluation of patients in a specialist center should revisit the history in detail and include a video-EEG to characterize and clarify the epilepsy type. Once the diagnosis of epilepsy is established, imaging studies must be scrutinized in order to determine whether an epileptogenic focus exists, in order to facilitate a possible surgical work-up. For a magnetic resonance imaging (MRI) of brain to be considered normal, the study must be acquired with a dedicated epilepsy protocol and interpreted by an experienced neuroradiologist. If no focus is found on MRI, other ancillary tests include positron emission tomography, ictal single-photon emission computed tomography, and magnetoencephalography. Functional studies such as functional MRI can be used to study eloquent regions of the brain. If localization is not clear, or the relationship of eloquent cortex to epileptic cortex needs to be more precisely defined, invasive testing can be considered. Options in this circumstance include subdural electrodes, depth electrodes, or a combination of both. Psychiatric evaluation and neuropsychologic testing is usually always warranted in the presurgical evaluation of the patient.[57] The importance of psychiatric evaluation and ongoing management postoperatively cannot be emphasized enough with many patients remaining psychiatrically unwell. One study has reported ongoing use of psychotropic medication in up to 22% of patients at 24 months postsurgery.[58]

Treatment

Treatment with AEDs is standard care for patients with DRE, but successful outcomes with this approach alone are disappointingly small.[59] Uncertainty about how much the

apparent efficacy of AED treatment can be directly attributed to the AED and how much is attributed to a placebo effect remains an important issue. Epilepsy surgery should be considered for lesional partial epilepsy, as this has the greatest chance of producing remission. Other treatment modalities include electrical nerve stimulation and diet therapies, but these are more likely to be palliative, rather than curative, treatment options. Recently receiving great attention is the possibility of cannabis being useful in DRE management, with its exact role and success as a viable treatment option yet to be determined. Finally, treatment should not be restricted to only the achievement of seizure freedom, and must include the management of medical, neurological, psychiatric, and cognitive comorbidities. The following is a formulation of practice recommendations for patients with DRE.

AED treatment

Basic principles of epilepsy management and drug choices must firstly be applied. For example, medications such as CBZ, gabapentin, and oxcarbazepine would not be used for primary generalized epilepsy as they have poor efficacy. Similarly, certain AEDs have been identified to worsen underlying seizure control, such as LTG and gabapentin worsening myoclonus. Other considerations when choosing an AED include sex, fertility, age, body weight, interaction with other medications, and concomitant diseases. Often overlooked, the expense, availability, and ease of use of AEDs are equally as important when addressing lifestyle factors in the individual. Past treatment trials should also be revisited, with the dose and frequency of dosing evaluated to ensure that true treatment failure has occurred.

When considering an AED to be added, it should be noted that the likelihood of seizure freedom does not differ substantially between established and new-generation AEDs.[9] It may be beneficial to choose an AED with a mechanism of action that differs from a previously non-efficacious AED. Some evidence exists to support use of combination therapy with two or more anticonvulsants with different mechanisms of action acting in a synergistic manner but also reducing side effects. For example, combining VPA and LTG in partial and generalized epilepsy is an example of rational polytherapy that may be beneficial.[60] Other examples include combining VPA with ethosuxamide for childhood absence epilepsy,[61] and LTG with topiramate for a range of seizure types.[62]

If a patient has already failed two or more AED regimens, any sequential drug trial only has a small likelihood of inducing remission, with only 4%–6% per year.[63] Similarly, long-term follow-up studies have found that the small benefit of seizure remission in this group is not sustained in ≥25%.[64] However, even in the absence of complete seizure remission, a reduction in seizure severity may still be useful to the patient in improving quality of life,[65] and is worth considering. Overall, lack of success with a second AED should prompt the physician to either reevaluate the diagnosis or refer the patient to a tertiary epilepsy clinic for exploration of management alternatives such as surgery.

Surgical treatment

Upon a diagnosis of DRE, epilepsy surgery should be considered, as in some cases, delaying surgery may actually worsen the chances of postoperative seizure freedom.[66] The greatest rate of success from surgery has been shown in patients with MRI lesions that are concordant to the epilepsy. These patients are more likely to be seizure free following epilepsy surgery, than those undergoing surgery with a normal MRI.[67] However, a normal MRI should not preclude surgical evaluation as favorable outcomes in this group are still possible.[68]

Lesions that are commonly resected in focal epilepsy include but are not limited to hippocampal sclerosis and focal cortical dysplasia. The most common form of resective surgery in epilepsy is the anterior temporal lobe resection in mesial temporal lobe epilepsy, and this has been shown to be superior to medical therapy. Outcome data at 1 year have demonstrated that 58% of patients who underwent surgery were free of seizures impairing awareness, compared with only 8% in the medical arm.[69] This finding has been replicated in other trials. In the Early Randomised Surgical Epilepsy Trial (ERSET) study, 73% of patients who underwent epilepsy surgery (N=15) within 2 years of developing DRE were seizure free, compared to 0% in the medical arm (N=23) after 2 years of follow-up.[70]

Other surgical options include lesionectomy and multiple subpial transections, used when resection of the epileptic focus is not possible because of its proximity to eloquent cortex. Corpus callosotomy is used as a palliative tool and involves disconnecting pathways of seizure propagation in patients with significant cognitive impairment. Hemispherectomy (functional or anatomical) is reserved for epilepsy affecting an entire hemisphere, and is considered only when devastating epilepsy and preexisting neurological impairments, such as hemiplegia, visual field, or language defects, are present. Complications surrounding surgery can include but are not limited to perioperative infarcts, infection, and decline in memory.

Despite well-documented improved outcomes in several controlled trials, a 20-year delay still exists for the average patient with DRE to be referred to an epilepsy surgery center.[8,71] Once this occurs, the candidate's suitability for epilepsy surgery must be evaluated, and this requires a comprehensive, multiparametric, and multimodal approach for precise localization of the epileptogenic focus. In addition to demonstrating that the epilepsy is well localized based on testing, other factors need to be considered. These include whether the seizures are disabling, whether the location of the epilepsy is away from eloquent regions of the brain, and whether there are considerable risks to cognition and memory if surgery is performed.

Electrical stimulation therapy

There has been a recent resurgence for using brain stimulation for the treatment of epilepsy. This approach should be considered when the patient is not a suitable surgical candidate.

Vagus nerve stimulation (VNS) has been shown to decrease the frequency and intensity of seizures, with 30%–40% of patients achieving a >50% reduction in seizure frequency.[72] It should be considered in patients with DRE who are not good candidates for surgery or are opposed to it. It can also be considered in those who have not substantially improved following prior intracranial epilepsy surgery. The procedure involves implanting a VNS generator under the skin below the clavicle, with a stimulating wire from this attached to the vagus nerve. Precisely how VNS produces antiepileptic effects is unknown, but one mechanism involves desynchronization of thalamocortical activity that is mediated by the thalamic and brainstem nuclei.

Trigeminal nerve stimulation is another form of peripheral stimulation that has shown clinical efficacy in focal epilepsy.[73,74] Initially envisaged as an implantable system, with a VNS-like system providing regular stimulation to the first division of the trigeminal nerve, it proved as effective given as a scheduled overnight or evening program.[74,75] Further clinical trials are currently in progress, but this noninvasive system may offer similar efficacy as the VNS. As with VNS, a range of other effects have been observed, including improved mood.[76]

Another device gaining attention is deep brain stimulation, with open-label and some small controlled studies finding a reduction in seizure frequency by ≥50%.[77] Given its infancy in epilepsy management, these findings are promising, but long-term follow-up observations are lacking. More recently, a randomized clinical trial involving stimulation in the anterior nucleus of the thalamus (SANTE trial) was performed in 110 DRE patients, with some long-term data supporting safety and efficacy.[78] Seizures that were most drastically reduced by stimulation were focal dyscognitive and "most severe" seizures. Reported adverse effects included depression and memory problems. Complications included asymptomatic hemorrhages (5%) and implant-site infections (13%). At follow-up, an improvement in quality of life and seizure severity measures was noted. The rates of suicidality and SUDEP were comparable to the rates in the general DRE population. Future studies are necessary to identify a patient population for whom this technique is indicated. The mechanism behind success of deep brain stimulation in diminishing seizures is largely unknown, but has been hypothesized to involve stimulation-induced disruption of unopposed network activity.[79] As there are multiple potential targets and neural regions implicated in seizure propagation, the most efficacious target and optimal stimulation parameters are yet to be decided, with various targets currently being investigated.[80]

An alternative strategy is direct cortical or hippocampal stimulation, triggered by seizure activity. An implantable system developed by NeuroPace (CA, USA) consists of a device implanted in the skull which has sensing electrodes placed on cerebral cortex which are triggered by continuously monitored seizure activity.[81] Seizures are characterized for individual patients, and then tailored counterstimulation is delivered to the presumed seizure-onset zone. The electrodes can be a combination of hippocampal or cortical arrays, providing great flexibility in addressing potentially multifocal epilepsies. Pivotal clinical trials demonstrated convincing efficacy in a substantial proportion of individuals in a trial of refractory partial epilepsy.[82,83] Much is yet to be learned about optimal sensing and stimulation parameters, but these systems show much promise.

Finally, while not strictly a therapy, there is hope that intracranial EEG monitoring can be used in ambulatory patients with DRE, leading to more effectively timed therapies and better understanding of the natural history of a patient's epilepsy. Cook et al surgically implanted a seizure detection device in 15 patients with focal epilepsy, and collected data were used to predict periods of high, moderate, and low seizure likelihood in real time.[84] The device predicted impending epileptic seizures via a light display on the patient's handheld console, allowing patients some autonomy over timely seizure treatment and control over their disease. In addition to seizure prediction, it also provided constant EEG recordings, proposed to improve customized understanding of seizure

generation in the individual. The device is not clinically available, but the findings from this study outline the great potential of its use in the management of epilepsy. As with the NeuroPace system, significant new information regarding the patterns of seizure activity and the natural history have been revealed through these systems, leading to better understanding of the dynamics of the epileptic process.[85–87]

Diet therapy

The ketogenic diet was proposed as a treatment for seizures prior to introduction of modern AEDs.[88] The classic form of the diet is a high-fat, low-carbohydrate diet that induces urinary ketosis and mimics starvation while preserving necessary caloric intake.[89] The typical ratio of fat to carbohydrate and protein is 3:1 or 4:1. There is demonstrated efficacy in children with DRE, with more than one-third experiencing a ≥50% reduction in seizures.

Alternative diets to consider are the modified Atkins diet and low-glycemic-index diet.[90,91] In comparison to the ketogenic diet, the ratio of fat to carbohydrate and protein is closer to 1:1. Additionally, calories and fluid are not restricted. These have less gastrointestinal side effects due to using medium-chain triglycerides and long-chain fatty acids, but these versions do not achieve urinary ketosis to the same degree as the ketogenic diet. Nonetheless, in small case series of adult patients, the traditional ketogenic diet and a modified Atkins diet reduced seizure frequency by ≥50% in half of patients with DRE.[92] While these findings are encouraging, long-term outcome data report high dropout rates, with only 10% of patients remaining on the diet at 3–6 years.[93]

Cannabis

Recently, there has been intense interest regarding the potential of medical cannabis to treat seizures, due to mounting anecdotal reports and media coverage of its success. Additionally, in vivo preclinical studies suggest that cannabidiol (CBD), a non-psychoactive component of cannabis, has significant anticonvulsant effects, mainly in acute animal models of seizures.[94] Encouragingly, these studies have shown CBD to be similarly effective to the AEDs currently in clinical DRE use.[95]

To date, there are restricted data assessing chronic models of epilepsy as well as animal models of epileptogenesis. Some clinical evidence indicates that CBD is able to manage epilepsy in adults and children affected by refractory seizures, with a favorable side effect profile. Tzadok et al treated 74 pediatric patients, who were resistant to more than seven AEDs, with medical cannabis oil. The results were highly promising, with 89% of patients reporting a reduction in seizure frequency.[96] Conversely, seizure exacerbation after cannabis use has also been observed, and in this same study, 7% of patients reported this, leading to CBD withdrawal.

Further prospective randomized clinical trials are needed to prove or disprove the efficacy of CBD and to assess the long-term effects, particularly the neuropsychological effects in the developing brain. Systematic analyses in 2014 by the American Academy of Neurology and Cochrane Database both concluded that medical cannabis is of "unknown efficacy" to treat epilepsy,[97,98] with insufficient data to recommend its routine use. Nonetheless, CBD studies are underway, and this area of research remains exciting from a therapeutic point of view, as well as potentially increasing our mechanistic understanding of seizures.

Conclusion

DRE patients require a great deal of time and effort from treating physicians and also represent a huge economic burden. Coupled with significant psychosocial comorbidities and ongoing disability accumulated by ongoing seizures, management of DRE requires a multidisciplinary and often multitreatment approach with timely referral to specialist epilepsy centers for prompt evaluation. Along with these complex management challenges, unraveling the exact pathogenesis behind this disorder remains crucial to our understanding of DRE. The hope is that targeted treatment approaches will one day be available to help epilepsy patients who are diagnosed with DRE.

Disclosure

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