Introduction

Epilepsy: Diagnosis and Treatment in the 21st Century

By Martha J. Morrell, MD

Epilepsy is a neurological disorder that affects persons of all ages, persists for years (and even over a lifetime), and commits the individual to daily and often long-term treatment. Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment, although nonpharmacologic therapies occupy an increasingly important position.

As more AEDs become available, the challenge to the clinician is to choose the AED most likely to achieve seizure control with the least chance of acute or chronic toxicity. Thus, we consider safety as well as effectiveness. Effectiveness considers cognitive and sedating effects, effects on vision and coordination, impact on reproductive physiology, potential for teratogenicity, and effects on bone mineral metabolism. As AEDs are used for conditions other than epilepsy (ie, migraine, pain, bipolar disease, and depression), the concept of effectiveness remains relevant.

Beyond the seizure diagnosis, healthcare providers strive to establish a syndromic diagnosis. Establishing the epilepsy syndrome helps one identify probable etiology, predict response to therapy, and establish a likely prognosis. In this month’s first article, Dr. Jonathan Edwards discusses the classification of epilepsy syndromes, providing examples of some of the more common types. A proper organizational framework helps the clinician successfully direct the diagnostic evaluation of a patient. Diagnostic testing for seizures includes an electroencephalogram (EEG) and, for most, neuroimaging with magnetic resonance imaging (MRI).

Since 1993, with the introduction of 10 new AEDs, selecting a medication has been more challenging, but also more rewarding. Several of these agents have similar efficacy for given epilepsy syndromes, so selection must consider tolerability, ease of use, and pharmacokinetics. Dr. Carl Bazil’s article this month provides a thorough review of both the old and new AEDs. Considerations include efficacy for particular seizure types, acute toxicity, idiosyncratic reactions, chronic toxicity, teratogenicity, necessary dosing intervals, and likelihood of drug-drug interactions.

Nonpharmacologic therapies for epilepsy include surgery and vagus nerve stimulation (VNS). Surgery is the best chance for a cure in the 15% of patients who have surgically remediable epilepsy syndromes. These patients have discrete structural or functional lesions identified after an exhaustive evaluation that includes video-EEG recording of seizures, neuroimaging, neuropsychological assessment, language and memory lateralization, and an intracarotid amobarbital procedure. Properly identified candidates for cortical resection have a greater than 80% chance of permanent seizure remission.

Not everyone is a candidate for surgery. For those with medically refractory epilepsy who are not candidates for curative epilepsy surgery, VNS provides an exciting new option.

The vagus nerve stimulator is the first device approved by the United States Food and Drug Administration for the treatment of epilepsy as adjunctive therapy with AEDs. The device provides preprogrammed electrical stimulation to the ascending vagus nerve. Many patients experience seizure reduction and may also feel brighter and more alert. Open data suggest there may be a positive impact on affect in some patients.

In this issue, Dr. Steven Karceski examines the efficacy of VNS compared to corpus callosotomy in treating Lennox-Gastaut syndrome (LGS), a medically intractable epilepsy syndrome characterized by developmental delay and severe mixed seizures, including tonic and atonic seizures and generalized tonic-clonic seizures. In the past, those with LGS and seizures associated with injury could undergo resection of the anterior two thirds of the corpus callosum. This procedure limits the capacity of the seizure to spread from its region of onset to the contralateral hemisphere. However, corpus callosotomy is a major surgical procedure that is only palliative, and it is associated with 10% to 15% significant morbidity. Therefore, there has been interest in whether VNS might provide similar or improved benefit in this patient population with less expense and less morbidity. Dr. Karceski has reviewed the literature and taken advantage of an ongoing registry of persons implanted with the vagus nerve stimulator to contrast outcomes of people with LGS after implantation with the vagus nerve stimulator and corpus callosotomy.

One area of concern for reproductive-aged individuals who must take AEDs is the effect of these drugs on fertility, reproductive health, and pregnancy outcome. Fertility rates are lower in persons with epilepsy, and one putative mechanism is reproductive endocrine disorders. The potential for AED-related reproductive dysfunction might be mitigated by AED selection. Changes in reproductive steroids are a consequence of AEDs that alter steroid metabolism by the cytochrome P450 (CYP) enzyme system. My colleagues and I review here some of the reproductive health risks for women with epilepsy and present data demonstrating differential effects of individual AEDs on sex-steroid hormone concentrations. AEDs that induce CYP enzymes were associated with significant reductions in estrogens and androgens. The CYP enzyme inhibitor VPA was associated with significant elevations in androgens. AEDs which do not alter CYP enzymes were not associated with any change in steroid hormones, suggesting that some AEDs may be less likely to cause reproductive endocrine disturbances.

Epilepsy is a chronic illness. Patients deal with the burden of daily treatment and the potential for lasting side effects, including poor reproductive health. They also face significant social stigma. Any strides healthcare providers make towards reducing this burden and minimizing the negative impact of seizures and treatment will be well done.