Options for Pharmacoresistant Epilepsy in Children: When Medications Don’t Work

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Abstract

Medications are often first-line treatment for epilepsy in children. A detailed review of antiepileptic drugs and their application in various epilepsy syndromes is provided in the article “Antiepileptic Drugs—A Review” by Sankaraneni and Lachhwani (this issue). Here, we will focus on nonmedicinal approaches—some fairly longstanding and described since Biblical times such as the ketogenic diet while others are relatively new such as neurostimulation. Yet, others such as cannabinoids have been utilized for centuries for their medicinal properties, but we are just learning the scientific basis behind their efficacy. Families are often interested in nonmedicinal avenues of treatment, and knowledge of these options can empower a pediatrician to help families make choices that have scientific validity. [Pediatr Ann. 2015;44(2):e43-e48.]
Despite the significant development and release of a number of antiepileptic drugs (AEDs) over the past 20 years, at least 20% of children with epilepsy today are pharmacoresistant. Children with more difficult to control epilepsy syndromes such as West, Lennox-Gastaut, and Dravet tend to have frequent seizures and marked developmental compromise. Symptomatic focal epilepsy is also associated with higher rates of medical intractability. In clinical practice, when seizures are not readily controlled, it is common to titrate to a maximal AED dosage and/or multiple combined AEDs in an attempt to maximize seizure control. In most cases, regardless of etiology and epilepsy/seizure type, uncontrolled seizures combined with maximized AED therapy tend to have a negative impact on cognitive development, behavior, education, psychosocial well-being, and quality of life. There is also increased risk for physical injury, aspiration, and sudden unexpected death in epilepsy. When seizures are pharmacoresistant or adverse effects of AEDs are unacceptable, we begin to consider alternative therapeutic options that include ketogenic or modified Atkins diet, vagus nerve stimulation, or epilepsy surgery. Children with pyridoxine dependency and cerebral folate deficiency respond favorably to supplementation with pyridoxine and folinic acid, respectively. Parents or caregivers may also begin to explore other alternative options such as dietary changes, herbal or nutritional supplements, and others. Recently, cannabidiol treatment for use in children who are pharmacoresistant has attracted much attention, and is being tried where it is legally available. There are alternative therapies available for children with uncontrolled seizures with a proven record of success, and newer options where further evaluation is warranted.

**ALTERNATIVE TREATMENT OPTIONS**

**Pyridoxine and Folinic Acid**

Pyridoxine-dependent epilepsy was first recognized to be responsive to supplemental pyridoxine or vitamin B6 in 1954. With this rare disorder, seizure onset occurs most commonly in neonates and infants who respond poorly to AED therapy. For five decades, this diagnosis was made based on a clinical response to a trial of pyridoxine therapy. In responders, discontinuation of pyridoxine results in recurrence of seizures and lifelong therapy is warranted, thus the term pyridoxine dependency. Recently the responsible enzymatic and genetic defects were finally discovered. There is a deficiency in alpha-aminoadipic semialdehyde dehydrogenase or antiquitin, which is coded for by the ALDH7A1 gene. The deficiency results in accumulation of piperidine-6-carboxylic acid that inactivates pyridoxal-phosphate. A number of ALDH7A1 gene mutations have been identified and can be detected with mutation analysis. Folinic acid-responsive seizures are also caused by mutations in this gene, and a subset of patients also require folinic acid supplementation. Recent work indicates that a diet low in lysine may also be beneficial for children with pyridoxine dependency.

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**Diet Therapy**

The ketogenic diet (KD) and modified Atkins diet (MAD) are now considered to be standard alternative therapies for the treatment of epilepsy in children. This is not novel therapy. Fasting was suggested to prevent seizures by Hippocrates, and in the Bible in the book of Mark. In the first published report in 1921 regarding the use of the KD to treat epilepsy, Dr. Robert Wilder aptly noted that the success of the diet was greatly dependent on the intelligence of the mother. In other words, the diet was difficult to plan, administer, and adhere to. However, today we have much more knowledge and information available concerning the nutritional content of almost every food item, which allows accurate counting of carbohydrate grams. Commercially prepared ketogenic formulas are also available. This has made KD and MAD management much more practical and popular. It is still not easy though, and strict diet adherence is absolutely necessary to achieve the proper level of ketosis and clinical efficacy.

The basis of the classic KD is a 3:1 to 4:1 ratio of fat to protein plus carbohydrate. The drastic restriction in carbohydrate consumption results in a marked decrease in glucose utilization, and a conversion to the production of ketone bodies from fatty acid energy production. Evidence supports the notion that ketone bodies have a direct antiepileptic effect in the brain via multiple mechanisms that may include disruption of glutamatergic synaptic transmission, inhibition of glycolysis, and activation of adenosine triphosphate sensitive potassium channels. Other diets are also used with
the same desired goal of ketosis. The MAD is not as restrictive as the KD and allows greater protein intake. Additional alternative diets include the medium chain triglyceride diet, low glycemic index diet, and other variations on the theme. The Atkins diet is a popular weight loss diet that many people are familiar with, but in order to achieve the desired level of ketosis needed to result in seizure control, carbohydrate intake is strictly limited to 10-20 grams per day with the MAD. In general, it has become most practical to use the KD for children who are either bottle or tube fed, and the MAD for older children and adolescents who are oral feeders. Hospitalization is typically preferred to initiate the KD to monitor for acute occurrence of hypoglycemia and/or acidosis. The MAD is commonly initiated on an outpatient basis. The impact on seizure control is similar with both diets, with resultant >50% reduction in seizure frequency in about 50% of patients, >90% reduction in 30%, and seizure freedom in 15%.1,9 Initiation of these diets commonly induces a brisk response in those who are going to respond (usually within 2 weeks), but it is recommended to maintain the chosen diet for a 3-month period prior to discontinuation due to lack of efficacy. When seizures are controlled or significantly reduced in response to diet therapy, it may be appropriate to serially decrease or even discontinue AEDs. Multivitamin supplementation should be provided with these diets in formulations that do not include sugar or significant amounts of carbohydrate. All AEDs and other medications also need to be sugar-free. In general, KD and MAD are well tolerated, but gastrointestinal side effects may occur including constipation, diarrhea, nausea, and vomiting. Poor weight gain or even weight loss are common. With long-term use, there is an increased risk for development of renal stones and bone fractures, but significant dyslipidemia is uncommon.11 The KD is contraindicated in children with mitochondrial disorders and porphyria.12

Discontinuation of the KD/MAD in responders is usually considered after 2 years. Long-term continuation can be considered especially when there is a marked response with >90% reduction in seizures despite a persistently epileptiform electroencephalography (EEG). Ultimately, discontinuation of the diet is usually performed gradually over 2-3 months.13

A gluten, casein-free diet has been advocated as potentially helpful anecdotally, but there are no large-scale scientifically-controlled studies that document efficacy in children with epilepsy.

Neurostimulation

Another therapeutic option for children with pharmacoresistant epilepsy is vagus nerve stimulation (VNS). In 1997, VNS was approved by the US Food and Drug Administration (FDA) as adjunctive therapy for focal onset seizures in patients older than age 12 years. Since then, there has been extensive use of VNS in children, including many under age 12 years. The VNS device is implanted subcutaneously typically beneath the left clavicle. A lead wire is tunneled subcutaneously up the neck, and the lead is placed around the left vagus nerve. The device is programmed externally to deliver pulses of electrical stimulation at regular time intervals. Typical initial settings include an on-time of 30 seconds and an off-time of 5 minutes. Based on the response to stimulation, the settings can be adjusted accordingly over time by increasing the current and/or duty cycle (the percentage of time during which stimulation is active). Higher duty cycles of >40% are commonly used for more refractory patients, but a duty cycle of >50% is not recommended due to increased risk of nerve injury. Rapid cycling with brief on-times and off-times may be more effective in some patients.

The mechanism of action of VNS in seizure prevention is not completely understood. A number of studies have evaluated the effect of VNS in animal epilepsy models as well as humans. Positive emission tomography (PET), EEG, and cerebrospinal fluid studies in humans indicate that multiple mechanisms are involved, and appear to include effects on the reticular activating system, central autonomic network, limbic system, and noradrenergic projection system. More exact mechanisms are only theoretical.14

It should first be understood that VNS is a palliative therapy aimed at reducing seizure frequency and severity. It rarely produces complete seizure freedom. In general, it is difficult to predict which patients will respond favorably to VNS. It is typically stated that the response follows a “rule of thirds”—with one-third achieving marked response, one-third a moderate response, and one-third a minimal or poor response. An evidence-based analysis of VNS in children with epilepsy indicated that 55% of 470 children with focal or generalized epilepsy achieved >50% reduction in seizure frequency.15 Response to VNS therapy has a tendency to continue to improve over time. During an aura or seizure, VNS stimulation can be activated by swiping a magnet over the implanted generator, which may abort the seizure in some patients. The most common complication following VNS placement is postoperative infection at the implantation site that typically necessitates device removal. Vocal cord paralysis occurs in about 1% of patients. Lesser adverse effects such as discomfort, cough, and hoarseness are usually transient.16
Deep brain stimulation for epilepsy has been studied primarily in adult patients with very little work performed in children. The FDA recently approved the Neuropace RNS System (NeuroPace; Mountain View, CA) as an adjunctive therapy for individuals with uncontrolled partial seizures older than age 18 years. More research is needed in pediatric patients.

**Epilepsy Surgery**

Surgical treatment for children with epilepsy is primarily considered when two or more AEDs have failed, the seizures are debilitating, and there is little chance of temporal resolution. Resective epilepsy surgery often offers the best possibility of seizure freedom in children with intractable focal onset epilepsy. The best results occur when the ictal focus (seizure generating focus) identified with EEG correlates with a structural abnormality identified with neuroimaging. High-resolution magnetic resonance imaging (MRI) may identify a low-grade tumor, cortical dysplasia, mesial temporal sclerosis, or other focal structural abnormalities that cause seizures. A prolonged video EEG with scalp electrodes is used to record clinical seizures and localize the ictal focus. It is common at this point to proceed to intracranial EEG with placement of one or more grids of electrodes over the cortical surface, or depth electrodes into the substance of the brain to record seizures for more definitive localization. Other modalities used may include PET, magnetoencephalography (MEG), single photon emission computerized tomography (SPECT), and other specialized modalities and techniques. MEG, PET, and SPECT findings can be superimposed on 3-dimensional MRI with co-registration for precise localization of the ictal focus.

Epilepsy of temporal lobe origin accounts for about 15%-20% of all cases of epilepsy in children, and is most amenable to surgical resection with resultant seizure-freedom rates of approximately 75%. Resistance to medication is more common with an associated structural lesion (low-grade glioma, cortical dysplasia, or sclerosis) within the mesial temporal structures, and resultant postsurgical seizure freedom is highest in these lesional cases at >80%.\(^{17}\) Extra-temporal focal epilepsy is more difficult to treat surgically, with resultant seizure freedom in approximately 60% of lesional and 40% of nonlesional cases.\(^{18}\)

Functional hemispherectomy or hemispherotomy can be considered as an option for children with refractory seizures associated with more extensive onset and/or structural abnormality within a cerebral hemisphere. Anatomic hemispherectomy involves the complete removal of one cerebral hemisphere. There are high rates of postoperative complications including intracranial hemorrhage and hydrocephalus. Functional hemispherectomy includes resection of a portion of the hemisphere commonly including the temporal lobe, and disconnection of the rest of the hemisphere. This leaves much of the tissue in place, but disconnected. Hemi- spherotomy takes this approach a step further with disconnection without significant tissue removal. Patients selected for these surgeries typically have a combination of frequent and debilitating seizures and contralateral hemiparesis. With functional hemispherectomy and hemispherotomy, the primary intent is disconnection resulting in the inability of ictal discharges arising from the abnormal hemisphere to produce clinical seizures. Resultant seizure freedom is achieved in approximately 60% of patients.\(^{19}\)

A palliative surgery can be considered for children with intractable epilepsy that is primarily generalized or of multifocal origin, or when the focus cannot be resected safely. Corpus callosotomy is primarily considered and preferred in cases of severe generalized epilepsy with frequent atonic seizures; for example, seizures characterized by sudden drops due to loss of muscle tone. These seizures are notoriously difficult to control, and commonly result in injuries and morbidity. Callosotomy results in a significant reduction in atomic seizure frequency of >90% in 80%-90% of patients, and complete control is often achieved.\(^{20}\) Callosotomy may likewise effectively reduce the frequency of generalized tonic seizures and secondary generalization of focal seizures. The primary risk of callostomy is production of a disconnection syndrome. This may include a mixture of deficits in speech and language, spatial orientation, motor control, vision, and hearing. An anterior callosotomy with sectioning of the anterior two-thirds is typically preferred over a complete callosotomy, and usually produces less functional deficits; however, complete callosotomy is more likely to produce the greatest reduction in seizures. A rational approach is to perform an anterior callosotomy first, and if seizures are not satisfactorily decreased, the callosotomy is completed with a second surgery. This two-stage approach also appears to decrease the risk for severe disconnection syndrome.\(^{21}\)

**Cannabidiol**

The use of cannabinoids to treat epilepsy is not exactly novel, but recent reports of several children with severe and debilitating pharmacoresistant epilepsy responding dramatically to marijuana extracts high in cannabidiol concentration, and the legalization of medical marijuana in some states have resulted in a frenzy of interest in this potential therapy. That interest may actually be well founded, but the safety and efficacy of cannabidiol therapy for epilepsy in children desperately needs to be properly vetted via scientific evaluation. It is important to recognize that cannabidiol is a nonpsychoactive phytocannabinoid, and therapeutic formulations can be pre-

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pared that do not contain tetrahydrocannabinol.

Animal studies have indicated a significant antiepileptic effect with cannabidiol. The FDA has granted orphan-drug designation to allow accelerated evaluation of cannabidiol in children with pharmacoresistant epilepsy, and a multicenter, open-label clinical trial was initiated in early 2014. The goal of this study is to enroll 150 patients ages 1-18 years with intractable epilepsies resistant to many therapies including AEDs and KD with intent to treat for 1 year. Preliminary results from this study were provided in a press release in June 2014. At that point, 27 children and young adults with severe epilepsy had completed a 12-week treatment phase with cannabidiol resulting in a 44% median overall reduction in seizure frequency. Essentially one-half of subjects achieved >50% reduction in seizure frequency including 22% who experienced a 90% reduction and 15% who became seizure-free. As noted in many of the anecdotal reports, cannabidiol appeared to be especially effective in children with Dravet syndrome (see article by Park and Shahid, this issue). In a safety group of 62 patients, 81% reported at least one adverse event, but 80% of those were considered mild. Although the positive aspects of this study are impressive, cannabidiol will not be effective for everyone with epilepsy. The next important step will be to proceed with double-blind, placebo-controlled trials.

Herbs and Other Alternative Therapies

When seizures are not controlled with traditional therapy, families may ask about or experiment with other alternative options. The use of herbal preparations to treat seizures dates back many centuries. In general, the use of herbal and nutritional supplements in our society is very popular. It is estimated that 1 in 5 of the United States population presently uses herbal supplements or remedies, although this number is lower in children. The Dietary Supplement Health and Education Act (1994) essentially ruled that herbal and natural products could be marketed without proven safety and efficacy, or significant regulation by the FDA. Today, many herbal preparations are touted as having antiepileptic properties, and many families of children with epilepsy are open to trying them. In general, however, there have been no scientifically performed studies documenting the efficacy of these agents for seizure prevention. A common misconception is that herbs are natural and therefore safe, but adverse effects can occur and an overdose can be dangerous with some herbal agents. Concurrent use of multiple agents may result in increased risks for adverse effects and toxicity.

Melatonin is commonly used as a sleep-aid in children, including those with epilepsy. Reports regarding the impact of melatonin on seizures are mixed. The best evidence indicates that melatonin improves sleep and appears safe in children with epilepsy, and may possibly have a positive impact on seizure control. Clinical trials are needed to better evaluate the impact of melatonin therapy on children with epilepsy.

Hyperbaric oxygen therapy has become popular with some families for the treatment of their children with autism, cerebral palsy, and other neurologic disorders. There are no published scientific studies that indicate a positive impact on seizure control, but oxygen toxicity-induced seizures in response to hyperbaric oxygen therapy have been reported.

Biofeedback and relaxation therapy may be beneficial in stress and anxiety reduction in older children with epilepsy and may have some benefit in that regard, but these modalities do not appear to be directly effective for suppression of clinical seizures. Claims have been made that chiropractic therapy may be useful for seizure prevention, but these claims appear unfounded and counterintuitive.

CONCLUSIONS

Despite the fact that a number of new AEDs have become available over the past 20 years, there has been little impact on the fact that 20% of children with epilepsy remain pharmacoresistant. In these children it is appropriate to consider alternative therapies. The greatest chance of achieving complete seizure control occurs in response to resective epilepsy surgery in patients with focal epilepsy when the ictal focus can be reliably localized and removed. Diet therapy with either the KD or MAD tends to be more palliative with approximately one-half of patients achieving a significant reduction in seizure frequency of >50%. VNS is another palliative option. Cannabidiol is a new emerging option and investigative studies will hopefully confirm a positive response, especially in children with some of the most severe forms of epilepsy such as Lennox-Gastaut and Dravet syndromes.

REFERENCES