ELSEVIER

Seminars in
Pediatric
Neurology

Nonpharmacological Treatment Options for Epilepsy

Raj D. Sheth, MD, Carl E. Stafstrom MD, PhD, and David Hsu MD, PhD

Approximately one third of children with epilepsy have persistent seizures despite trials of multiple antiepileptic medications. For some of these patients, epilepsy surgery may provide freedom from seizures. However, in many cases, epilepsy surgery is not a viable treatment option. Nonpharmacological approaches are a useful adjunct to help manage seizures in these children. This review examines the role of vagus nerve stimulation, the ketogenic diet, and various forms of EEG biofeedback therapy in children with intractable epilepsy. Although the mechanism of action is not known precisely for any of these adjunctive therapies, they add an important and evolving dimension to the management of difficult to control epilepsy in children. In addition, pyridoxine-dependent seizures are discussed as an example of an etiology of refractory seizures that responds well to replacement therapy.
Semin Pediatr Neurol 12:106-113

KEYWORDS **Intractable epilepsy, vagus nerve stimulation, ketogenic diet, pyridoxine dependency, biofeedback**

Approximately one third of children with epilepsy have intractable seizures. Medically intractable epilepsy in childhood is difficult to define and must take into account the natural history of seizures in childhood and the tendency for seizures to become less frequent and severe with passing age.[1] Nevertheless, the approach to intractability in childhood appears to be similar to that in adults. Despite the availability of newer antiepileptic drugs (AEDs), the rates of epilepsy intractability do not appear to have decreased.[2] The likelihood of controlling seizures after 2 appropriately chosen AEDs fail is low.[3] In most children, at least 3 AEDs should be tried before a child is said to have intractable epilepsy.[4] More than half of these patients will not be candidates for epilepsy surgery.

The effects of seizures on cognitive function in children with intractable epilepsy are particularly apparent when there is reversal of cognitive decline after successful control of seizures.[5,6] Patients with uncontrolled seizures experience a poorer quality of life, including poor self-esteem, higher levels of depression, and other limitations.[7] Vagus nerve stimulation, the ketogenic diet, and electroencephalogram (EEG) biofeedback offer adjunctive options to conventional AED therapies for children with intractable epilepsy. Hopefully, these options can restore some of the cognitive and behavioral deficits as well as reduce seizures.

Department of Neurology, University of Wisconsin, Madison, Madison, WI.
Address reprint requests to Raj D. Sheth, MD, Professor, Department of Neurology, 600 Highland Avenue, H6/574 CSC, Madison, WI 53792-5132. E-mail: sheth@neurology.wisc.edu.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) provides an adjunctive treatment option for children with refractory epilepsy who have either failed AED trials, in whom epilepsy surgery is not an option, or when families decline epilepsy surgery.[8,9] VNS is thus considered adjunctive to ongoing AEDs.[10]

Experiments by Zabara[11] showed that VNS may be a therapeutic portal to desynchronize electrocerebral activity. In those experiments, strychnine-induced seizures in dogs were reduced by VNS stimulation. Penry and Dean[12] and Uthman et al[13] reported on the first patient with intractable epilepsy who became seizure free after VNS. Subsequently, an implantable device was commercially developed to systematically stimulate the vagus nerve [NeuroCybernetic Prosthesis system (Cyberonics, Houston, Texas)]. The device consists of (1) an encased pulse generator/battery, (2) bipolar stimulating leads, (3) a handheld programming wand, and (4) a magnet with which to activate the device externally. The pulse generator is typically implanted below the left clavicle in the subcutaneous tissue of the upper chest and is connected to the left vagus nerve in the neck via the bipolar lead. Placement of the pulse generator varies; in young children, the pulse generator may be implanted in the abdomen to accommodate the generator, or, in women, for cosmetic reasons,

 1071-9091/05/$-see front matter
doi:10.1016/j.spen.2005.03.005

the device may be implanted lower anterior axilla beside the pectoral muscle.

Although there are currently other neurostimulation devices being developed for epilepsy, such as the anterior thalamic stimulation and the reactive neurostimulation (Neuropace, 1375 Shorebird Way, Mountain View, CA 94043, USA), VNS is the only nonpharmacological intervention that has been approved by the Food and Drug Administration. This approval is for the treatment of epilepsy in adults and adolescents over age 12 years. Since 1997, more than 10,000 patients have been implanted with the VNS. Although there is well-developed literature on its use in adults and older adolescents, there is also emerging literature on the role of VNS in childhood.[14]

Anatomy and Mechanism of Action

The vagus nerve (cranial nerve X) has widespread central and peripheral projections, including the amygdala, thalamus, nucleus of the tractus solitarius, and other cortical areas via the brainstem reticular formation.[10] The right vagus projects fibers to the sinoatrial node in the heart and the left vagus nerve to the atrioventricular node. In animals, stimulation of the right vagus nerve consistently produces a greater degree of bradycardia than when the left vagus nerve is stimulated. Postsynaptic projections from the medulla occur in the pons, thalamus, amygdala, and insula. The reticular activating system and the limbic system feature prominently in the activation of the vagus nerve. However, despite these widespread synaptic projections beyond the medulla, the exact mechanism by which VNS reduces seizures remains unknown.

Animal experiments have shown that VNS reduces penicillin-induced cortical interictal spiking rates by one third in rats.[15] In animals, the stimulation effect may increase or decrease EEG synchronization depending on the rate of stimulation. However, this mechanism does not appear to be the primary factor underlying efficacy and has not been shown in humans. VNS does not appear to exert its effect by a mechanism recordable by EEG. Changes in cerebrospinal fluid inhibitory amino acids have been noted with chronic VNS, although these changes were observed in both responders and nonresponders to VNS. An interesting clinical observation is the increase in antiseizure effect that occurs with time. This increased seizure control, which occurs 6 to 12 months after implantation, is also unexplained.

In humans, the central effects of VNS have been shown by positron-emission tomography. Henry and colleagues[16] recently showed that seizure control improved during a period when VNS-induced cerebral blood flow declined in cortical regions and proposed that altered synaptic activities at sites of persisting VNS-induced cerebral blood flow changes may reflect antiseizure actions of the VNS.

Efficacy, Tolerability, and Safety

Penry and Dean[12] initially showed that 4 of 11 patients with intractable epilepsy became seizure free after VNS. Early studies showed that a third of patients experienced a >50% reduction in seizure frequency. Patients randomized to high- versus low-stimulation groups showed similar rates of seizure control, with response rates up to 52% at 18 months after VNS.[17-21]

Two pivotal studies were evaluated by the United States Food and Drug Administration before VNS was approved for the treatment of epilepsy. The first multicenter trial (EO3) examined 114 patients over 12 years of age.[22] Prospective baseline seizure rates were compared with active stimulation. The high-stimulation group was programmed to receive stimulation for 30 seconds every 5 minutes with a dose range up to 3.5 mA. This group was compared with a low-stimulation group ("placebo") that received <3.5 mA of stimulation for 30 seconds every 1.5 hours. AEDs were kept constant during the trial. Thirty-one percent of the high-stimulation group had a >50% reduction in seizures compared with 13% of the low-stimulation group.

The second pivotal study (EO5) was performed in 199 patients followed for 3 months. Groups were divided into high- and low-stimulation parameters as described earlier. Twenty-eight percent of patients experienced a >50% seizure reduction in the high-stimulation group (95 patients) compared with 15% of the low-stimulation group.

Long-term follow-up studies have assessed up to 3 years of VNS stimulation in up to 440 patients.[23,24] Importantly, these studies found a progressive decline in side effects and also showed a tendency for greater seizure reduction with time. Although randomized, controlled trials restricted to childhood are not available, there were 60 patients aged 3 to 18 years in EO5. These children had a 23% reduction in seizures at 3 months that increased to 42% of seizure reduction at 6 months of VNS. Pediatric case series have shown highly variable efficacy rates of control compared with the adult series presented earlier.[18,25] Of 309 children between ages 3 and 18 years who were implanted at various centers across the United States, favorable response rates (>50% seizure reduction) were seen in 19% to 53% of patients followed between 3 months and 24 months.[14]

Surgical Considerations and Complications

The VNS is attached at the midcervical portion of left vagus nerve, chosen because it is relatively free of branches and lies within the carotid sheath. Typically, implantation takes 2 hours; patients are usually observed overnight after implantation and are administered antibiotics for 24 hours. The overall infection rate is 3%. Many patients are successfully treated with antibiotics, although 1% must have the device removed.

The recurrent laryngeal nerve travels with the midcervical portion of the left vagus nerve and is also stimulated, accounting for the hoarseness that occurs each time the device is triggered. Vocal cord paralysis is the most common surgical complication, occurring in about 1% of patients in the E05 study. Vocal cord dysfunction is suspected if the patient presents with persistent hoarseness or dysphagia. Vocal cord dysfunction is minimized when care is taken to avoid nerve retraction and damage to the vascular supply of the nerve. Avoidance of high-stimulation intensities may also help re-

duce the degree of vocal cord dysfunction. Other less frequently occurring complications include Horner's syndrome, facial weakness, breakage of the leads, and bradycardia.[19-21]

Initiation and Maintenance Parameters

After implantation, the device is typically turned on in the operating room to deliver a stimulation of 0.25 mA. Thereafter, the stimulation is increased in 0.25-mA increments until seizures respond or intolerable side effects appear. Concomitant AED therapy is kept stable for 12 weeks while the device is being ramped up before a reduction in the dosage or number of AEDs is considered. Current generator batteries are expected to last 10 years, although this is very dependent on stimulation parameters.[18]

Advantages and Disadvantages of VNS

Major disadvantages of the VNS are the cost of the device and the need for its surgical implantation. Furthermore, one third of patients will experience no benefit from VNS, and only a few patients experience complete seizure freedom. Unfortunately, it is not possible at present to identify which patients are most likely to benefit from the VNS. Advantages of VNS include the absence of cognitive side effects, which are so common with AED treatment. In some patients, a reduction of the number or dosage of concomitant AEDs is welcome. The availability of a relatively straight forward alternative therapy in patients who are not surgical candidates is an added advantage.

The Ketogenic Diet

By now, the ketogenic diet (KD) is familiar to most physicians caring for children with epilepsy. The KD is a high-fat, low-carbohydrate, adequate-protein regimen that has been used for almost a century to treat children with medically refractory epilepsy. It is important for pediatric neurologists to understand the indications and uses of the KD and how to select the patients who will most benefit from it.

The KD, originally devised in 1920 by Wilder,[26] was intended to mimic fasting, which had been known for centuries to improve seizure control in persons with epilepsy. With the advent of anticonvulsant medications in the mid and late 20th century, the KD was relinquished to the back closet of most epilepsy clinics. However, in the early 1990s, the KD experienced a resurgence, and it now holds an important place among therapies for refractory epilepsy in children (and increasingly in adults).

Here, we briefly review the scientific basis for the KD, describe recent studies of its efficacy, and discuss precautions that need to be considered before initiating the KD. Information about other aspects of the KD are available in recent reviews, including its history,[27,28] possible mechanisms of action,[29-32] details of administration,[33,34] and complications.[35,36]

Efficacy of the KD

Numerous early reports attest to the effectiveness of the KD in small, uncontrolled series of patients.[37-39] Most of these reports, published in the 1920s and 1930s, are anecdotal. Importantly, clinical details are lacking, and the seizures are not characterized according to the modern classification. Nevertheless, at least one third of treated children had "good" or "excellent" responses to the diet, usually defined as at least a 50% reduction in seizures.

In the modern era, the effectiveness of the KD has been confirmed, both in the United States and internationally.[40-44] The current success rate of the KD in controlling refractory seizures is at least as good and often better than that of the "new" antiepileptic medications.[41] In general, at least half of all patients treated with the KD will exhibit a 50% or greater reduction of seizure frequency. Any seizure type may respond to the diet;[45] some generalized seizure types (myoclonic, atonic, generalized tonic-clonic, and even infantile spasms[46]) may respond preferentially. The KD works in all ages, from infancy through adulthood, although it may be maximally effective in the toddler and school-aged child.[47-49] Perhaps most importantly, there is intriguing recent data that KDs can sometimes be discontinued without concomitant loss of seizure control.[33,50] This observation suggests that the KD might be both anticonvulsant (stops seizures) and antiepileptogenic (retards the development of epilepsy).

A multicenter study of KD efficacy, involving 7 comprehensive epilepsy centers that studied 51 children, concluded that more than 40% of children had at least a 50% decrease in seizure frequency when evaluated after 1 year on the diet.[40] The study found no relationship between KD efficacy and the age at diet initiation, seizure type, or EEG findings. Although this study was not randomized or blinded, it showed that the KD could be successfully applied in a wide variety of clinical settings and in geographically diverse medical centers.

A large, prospective study of KD efficacy in 150 children (mean age, 5.3 years) with intractable epilepsy of different types was conducted at John Hopkins Hospital.[51] These patients were extremely refractory, averaging more than 400 seizures per month, and were treated with an average of 6.2 medications before the KD. Half of the children had a long-lasting decrease in seizure frequency of over 50%. Thirty children had a greater than 90% seizure reduction, and an additional 7 children became seizure free.

The same population has now been followed for up to 6 years, with impressive results.[50] Twenty children remain seizure free; only 1 is still on the KD, and the other 19 have been able to discontinue it and remain seizure free. An additional 21 children had a greater than 90% reduction in seizure frequency. Those who discontinued the diet had a lack of response, considered it too restrictive, or had complications at times of intercurrent illnesses. In addition to seizure control, many children were able to reduce or discontinue their standard anticonvulsants, with concomitant improvement in alertness and cognitive function and fewer anticonvulsant-related side effects.[52]

Despite the theoretical and practical difficulties of designing a blinded, crossover study of KD efficacy, such a study has been completed and is now being analyzed.[53] Children with frequent atonic seizures (most with Lennox-Gastaut syndrome) received 24-hour video EEG to quantify baseline

seizure frequency. The children were then randomly assigned either to the KD or to an identical KD with glucose added (to negate the ketosis). In the KD treatment arm, placebo (artificial sweetener) was added; this did not counteract the ketosis but made the diet equally "sweet" as the glucose-added arm. After a week on the respective diets, the groups were fasted briefly then crossed over to the other treatment. Video EEG data were also collected before and after the 1-week crossover phase. The data from this study should provide important information regarding the short-term role of the KD (and ketosis) in atonic seizure control.

The beneficial effects of the KD on seizure control, cognitive function, and neural development have been abundantly documented. The KD is effective across the age spectrum, from infants to adults, although it might work best in young and school-aged children because of better efficiency of ketone extraction by the brain at younger ages. Finally, a broad spectrum of seizures and epilepsy syndromes is amenable to KD treatment.[33,45]

Mechanism of Action

It is not known how the KD works. A reasonable hypothesis is that ketosis, a result of the ingestion of ketogenic foods, plays some role in seizure suppression. Human and animal studies support the notion that ketosis is necessary but probably not sufficient for KD effectiveness.

In a child on the KD, the brain switches from utilization of glucose to fat as the main cerebral energy source. When glucose is not available, such as during fasting or the KD, fatty acids are oxidized in the liver to ketones (beta-hydroxybutyrate, acetoacetic acid, acetone). The liver lacks the enzymes to degrade these ketones so they enter the bloodstream and circulate to tissues where they can be metabolized to energy (eg, brain, muscle). The brain can extract and break down ketones, which are then funneled into the tricarboxylic acid cycle and then to the electron transport chain, with resultant energy production.

Ordinarily, the brain uses glucose exclusively for its energy. There is a very small arterial-venous gradient for ketones under ordinary dietary circumstances. However, during fasting or KD feeding, this gradient increases and ketones enter the brain across the blood-brain barrier, using a monocarboxylic acid transport system. Therefore, during ketosis, the brain uses ketones as its energy source.[54] Exactly how this metabolic transformation from carbohydrates to ketones for energy leads to an antiepileptic effect is currently unknown. Possibilities include the alteration of the brain's "energy charge" (energy reserve or adenosine triphosphate/adenosine diphosphate ratio),[55] a direct effect of ketones on the excitability and synaptic function of neurons[31,56,57] enhancement of γ-aminobutyric acid (GABA) synthesis or function,[58] mitochondrial dysfunction,[59] or restriction of total calorie consumption.[60] Other mechanisms that have been considered in the past include acidosis, dehydration, elevated lipid levels, and electrolyte derangement,[61] but none of these hypotheses has stood the test of time. At present, there is intense laboratory effort to uncover the mechanism of action of the KD.[29,31,62] Hopefully, such information will lead to optimization of the administration, formulation, and composition of the KD.

Clinical Use of the KD

Much of the current protocol for KD treatment was developed in the 1920s. Therefore, even the modern use of the diet is based on lore as much as on scientific principles. Numerous clinical questions remain about the use of the KD. For example, is a fast necessary?[63] Which patients are most likely to benefit from the KD? How soon should the KD be begun in the course of a child's epilepsy? To date, children have been placed on the diet when all other options have failed. However, it might be possible to achieve the seizure control at an earlier stage in the child's epilepsy course, before exhausting all standard anticonvulsants.

In some medical conditions, KD treatment is essential. For example, glucose transporter defect (GLUT-1 deficiency)[64] is a genetic deficiency of the protein that transports glucose from the blood into the central nervous system. Therefore, affected children cannot use glucose properly for cerebral energy. The clinical presentation of this syndrome usually involves developmental delays and seizures. Children with GLUT-1 deficiency require the KD to provide sufficient energy for cerebral function.

In other disorders, including pyruvate carboxylase deficiency, fatty acid oxidation disorders, mitochondrial disorders, and carnitine deficiency, the KD could lead to neurologic deterioration.[36] In these disorders, switching to fats as the primary energy source could stress the body's metabolic regulatory systems and lead to energy failure.

KD Formulation

There are several alternative KD formulations, but the classic diet consists of a 4:1 ratio (by weight) of fat [protein + carbohydrates]. A dietitian familiar with the KD needs to teach the family meal plans and calculate appropriate dietary needs for each child.[34] Attention must be paid to total calories, sufficient protein for growth, and appropriate vitamins and minerals, in addition to maintaining the strict ratio of dietary components.[65]

An alternative formulation, involving medium chain triglycerides (MCTs), was previously popular.[66] The MCT diet produces an equivalent degree of ketosis with a less restrictive fat to carbohydrate ratio. By allowing a greater amount of carbohydrates, the MCT diet is more palatable, but it often results in bloating and severe diarrhea and is rarely used today.

The KD is most commonly initiated during a 3- to 5-day hospitalization. The diet begins with an initial fast, with modest fluid restriction to about 75% of maintenance. Once urinary ketones reach the 60 to 80 mg/dL range, the diet is started at a 4:1 ratio, with one third of the total calories as ketogenic eggnog on day 1, two thirds of total calories on day 2, and the full calorie diet on day 3. After that, ketogenic meals are started. Some centers successfully initiate the KD on an outpatient basis,[67] although hospitalizing children al-

lows for monitoring potential side effects during the fasting and the initial KD administration, including dehydration, hypoglycemia, and other metabolic problems.

Complications of KD Use

The KD is a form of medical therapy, not a fad diet. Although relatively safe in experienced medical hands, many potential side effects must be watched for. Renal stones develop in up to 7% of children on the KD.[68] Many children on the KD have reduced bone mass, and growth must be monitored carefully.[65] Interestingly, long-term atherogenic complications in children treated with this high-fat diet have not been reported.[69] It must be stressed that with close monitoring, the KD is safe in the vast majority of children.[33]

Some serious adverse events have been reported in children on the KD. In 1 study, 5 of 52 children on the KD developed hypoproteinemia, lipemia, hemolytic anemia, renal tubular acidosis, or elevated liver transaminases.[35] Many of these side effects were attributed to concurrent valproic acid use; this anticonvulsant must be used with caution with the KD.

For optimal administration of the KD, an interdisciplinary program is recommended, involving the coordinated care of a child by a team of health care professionals including the neurologist, dietitian, nurse, and social worker.[70] Before initiating the KD, parents must be fully committed to this intensive approach.

The Atkins Diet

The KD is the best known dietary therapy for epilepsy, but other dietary approaches may also be beneficial, including the Atkins diet (AD), calorie restriction, and a diet high in polyunsaturated fatty acids.[71,72] The AD induces a state of ketosis by providing high fat and little carbohydrates.[73] Therefore, it is theoretically possible that the AD could suppress seizures by a mechanism similar to the KD. There are 2 main differences between the diets (Table 1). First, the AD does not restrict calories. Second, the AD allows large amounts of protein, which is restricted in the KD. Other potential benefits of the AD are that a fast is not needed to start the diet, fluids are not restricted, and the diet can be begun by parents at home (although medical supervision is highly recommended).

A small recent case series reported the effectiveness of the AD on seizure control in 6 patients with refractory epilepsy, ranging in age from 7 to 52 years.[74] Two children and 1 teenager had a greater then 90% seizure reduction. No subject developed significant side effects such as hypercholesterolemia or excessive weight loss. All 3 of the successfully treated patients were able to taper their standard anticonvulsants. Although this is a small, uncontrolled series, it raises the possibility that the AD may be beneficial for children with medically refractory epilepsy. Children who withdraw from the KD usually do so because of poor tolerability or the family's inability to maintain the rigorous dietary regimen.[50] Therefore, a dietary regimen that increases palatability through less restrictive protein and calorie requirements might enhance patient compliance. Finally, because both diets induce ketosis, they may share a similar mechanism in seizure attenuation.

Table 1 Comparison of Ketogenic and Atkins Diets

Diet Composition	Ketogenic Diet	Atkins Diet
Fat (% by weight)	80	60
Protein (% by weight)	15	30
Carbohydrate (% by weight)	5	10
Calories (% recommended daily allowance)*	75	Not restricted

*Flexibility exists according to the patient's basal metabolic rate, age, and activity level.

Pyridoxine-Dependent Seizures

Pyridoxine (vitamin B6) terminates seizures in 2 forms of epilepsy: pyridoxine-dependent epilepsy and pyridoxine deficiency. In pyridoxine deficiency, a single dose of pyridoxine is sufficient to abolish seizures. In pyridoxine-dependent epilepsy, life-long treatment is necessary.

Symptomatic dietary pyridoxine deficiency is rare in the United States. However, drug-induced deficiency does occur, particularly with isoniazid therapy, which inactivates pyridoxine and at high doses can cause refractory seizures with severe acidosis, coma, and death. A single dose of pyridoxine by injection can reverse this isoniazid-induced pyridoxine deficiency syndrome.

Pyridoxine-Dependent Epilepsy

Pyridoxine-dependent epilepsy is a rare autosomal recessive disorder with birth incidence estimated at 1 in 783,000. Fewer than 100 cases have been described.[75] Seizures typically start prenatally or in the immediate postnatal period. The most common seizures types are focal or multifocal clonic seizures, often progressing to status epilepticus. Brief partial seizures, atonic and myoclonic seizures, and infantile spasms are also seen. Accompanying symptoms can include irritability, recurrent emesis, abdominal bloating, metabolic acidosis, and lethargy. Uncommonly, seizures may initially respond to traditional anticonvulsants or begin as late as 14 months of age.[75-77] Diagnostic criteria include seizures refractory to traditional anticonvulsants, complete seizure control on pyridoxine monotherapy, and recurrence of seizures when pyridoxine is withdrawn.

In pyridoxine-dependent epilepsy, glutamate levels are typically elevated in the cerebrospinal fluid, whereas GABA levels are depressed. Because glutamate is an excitatory neurotransmitter, and GABA is inhibitory, the result is excitotoxic injury and intractable seizures.[77] Early hypotheses focused on a possible defect of glutamic acid decarboxylase (GAD), which converts glutamate to GABA. However, attempts to show genetic linkage to brain isoforms of GAD have failed, whereas a linkage to chromosome 5q31 has been found. The gene and gene product are not known. Pyridox-

ine is phosphorylated in vivo to pyridoxal phosphate, which is a cofactor for GAD activity. Abnormal pyridoxal transport, binding to GAD, or other pyridoxal-dependent mechanisms have been proposed. There is no defect in pyridoxine uptake or metabolism.[76,77]

The interictal EEG can be normal in pyridoxine-dependent epilepsy, whereas runs of high voltage generalized rhythmic delta waves are suggestive of the disorder. Brain magnetic resonance imaging may show atrophy of both gray and white matter, mega cisterna magna, and thinning of the posterior third of the corpus callosum.[78]

Initial treatment consists of intravenous pyridoxine at 50 to 100 mg. Pyridoxine-dependent seizures usually stop within minutes but can take as long as hours. Oral maintenance doses vary widely, from 10 to 200 mg/d being typical, but much higher doses have also been used. Doses per body weight range from 0.2 to 30 mg/kg/d. Adverse effects of pyridoxine may include hypotonia, prolonged lethargy, and apnea. These adverse effects are thought to be secondary to increased GABA and decreased glutamate concentrations in the brain.

EEG Biofeedback Treatment of Epilepsy

EEG biofeedback is a form of operant conditioning that might be useful in the treatment of refractory epilepsy. This technique involves training patients to produce target changes on their EEGs. Target changes have included enhancement of the sensorimotor rhythm and reduction of the slow cortical potential (see later). In more holistic approaches, EEG biofeedback has also been used to teach subjects to relax by producing higher amplitude alpha waves.

Initial efforts in EEG biofeedback treatment for epilepsy focused on teaching subjects to enhance the so-called sensorimotor rhythm (11-15 Hz Rolandic waves), inspired by a serendipitous discovery that an analogous rhythm in cats protected against hydrazine-induced seizures (recounted in Sterman, 2000).[80] The sensorimotor rhythm is hypothesized to represent motor inhibition during alertness and has been linked to the gamma motor neuron-thalamocortical pathway. Although easy to detect using intracranial electrodes in cats, it is more difficult to detect in humans using scalp electrodes. Nonetheless, on the order of 66% of humans show an increase in the target frequency range after biofeedback training. Typical training sequences require 30-minute training sessions several times a week for 3 months or more.[80]

An initial study in a patient found that training initially increased power in the 8- to 15-Hz interval.[81] After further training, power decreased in the 8- to 11-Hz band but continued to increase in the 12- to 15-Hz band. Subsequent studies by multiple groups targeted enhancement of frequencies ranging from 8 to 18 Hz with little consistency across studies.[80] Some of these studies also trained subjects to decrease power in the 3- to 8-Hz range. Most of those 16 studies reviewed enrolled from 1 to 8 subjects, with the largest study enrolling 83 subjects. Controls included pretreatment baseline, noncontingent feedback, random feedback, and crossover design. The largest study (n = 83) was retrospective with target frequency range of 8 to 12 Hz (alpha rhythm).[82] This study did not document other therapeutic changes, such as anticonvulsant changes or levels. Subjects in all studies were designated as having refractory epilepsy, and the great majority had partial-onset seizures. If all of these studies are combined, 82% showed "clinical improvement."[80] However, for some of these studies (including the largest one), it is impossible to determine how many patients had a greater than 50% reduction in seizure rate and for what length of time. In one well-documented study using both random EEG feedback control and a double crossover design, 3 of 8 patients had a better than 50% reduction in seizure frequency with an average seizure reduction of 35%.[83]

Early criticism of sensorimotor feedback centered on the potentially confounding effect of nearby rhythms such as the mu and alpha rhythms.[84, 85] Given the variety of target frequency ranges used by various research groups, this criticism is still valid. Larger scale, more systematic studies are needed to establish the legitimacy of the sensorimotor feedback approach. However, active research in this area seems to have fallen off in the last 10 years.[80]

A slow, negative direct current potential shift is known to occur with seizure onset in humans and in animal models of epilepsy. This slow cortical potential (SCP) is thought to reflect apical dendritic depolarization of cortical pyramidal cells, which in turn represents a form of cortical excitation. It has been hypothesized that biofeedback training to regulate this SCP may decrease the rate of seizures. The contingent negative variation (CNV) is also a slow negative cortical potential that appears when a subject is primed to pay attention while awaiting a signal requiring a response. It has a wide field with frontal predominance and is thought to be a marker of cortical attention. The SCP seen with seizure onset may or may not have the same underlying neurophysiological basis as the CNV. Nonetheless, reducing the CNV has become the most recent paradigm for EEG biofeedback control of seizures.[86]

Interestingly, subjects without epilepsy are able to control the CNV (ie, to either increase or decrease its amplitude on command), after 2 training sessions of 1 hour each, but only 1 of 18 patients with epilepsy was able to do so in the same amount of time.[86] Subjects with epilepsy require about 10 training sessions before there is a trend toward control and another 10 sessions before the magnitude of change in the CNV is on the same order as the baseline CNV itself.

Rockstroh and colleagues[86] trained 25 patients with refractory epilepsy over 28 one-hour EEG training sessions to decrease the CNV and at 1 year found 10 of 18 patients with greater than 50% reduction in seizure frequency, of whom 6 were seizure free. Furthermore, there was a correlation of seizure frequency with control over the CNV. Those who failed to respond tended to have a larger baseline CNV.[87] The best response to CNV training were those with simple partial seizures, as opposed to complex partial or secondarily generalized seizures.[88]

The galvanic skin response (GSR) measures electrical resistance of the skin of the hand and is thought to be a peripheral measure of sympathetic arousal. Higher resis-

tance is correlated with an autonomically relaxed state, whereas lower resistance is correlated with a more aroused state. Higher cortical arousal as measured by a large-amplitude CNV (see earlier) is associated with lower peripheral autonomic arousal and vice versa. Assigning 18 patients with refractory epilepsy to GSR biofeedback training (n = 10) and sham control biofeedback (n = 8), Nagai and colleagues[89] found 60% of patients in the treatment group had a greater than 50% reduction in seizure frequency, a statistically significant difference compared with the control group. The reduction in seizure frequency in the treatment group was correlated with the degree of GSR control (rho = 0.7, $P = .001$).[90]

Holistic Approaches

EEG biofeedback relaxation training is popular outside of traditional neurology practices. The current evidence is that relaxation and cognitive behavioral training improve quality of life but neither reduces seizure frequency significantly.[91]

Future Directions

Reducing the CNV appears to be the most reproducible target for EEG biofeedback training. The attractiveness of EEG biofeedback lies in its lack of adverse effects. However, the time-intensive nature of EEG biofeedback training will likely limit its applicability to those with refractory partial-onset epilepsy who are not surgical candidates or to those who for lifestyle reasons have strong aversion to anticonvulsant therapy. The application of such techniques in children awaits further study.

References

1. Camfield C, Camfield P, Gordon K, et al: Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. J Pediatr 122:861-868, 1993
2. Pellock JM: Managing pediatric epilepsy syndromes with new antiepileptic drugs. Pediatrics 104:1106-1116, 1999
3. Camfield PR, Camfield CS, Gordon K, et al: If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr 131:821-824, 1997
4. Camfield PR, Camfield CS: Antiepileptic drug therapy: when is epilepsy truly intractable?. Epilepsia 37:S60-S65, 1996 (suppl 1)
5. Shields WD, Shewmon DA, Chugani HT, et al: Treatment of infantile spasms: medical or surgical? Epilepsia 33:S26-S31, 1992 (suppl 4)
6. Chugani HT, Shewmon DA, Shields WD, et al: Surgery for intractable infantile spasms: neuroimaging perspectives. Epilepsia 34:764-771, 1993
7. Dunn DW, Austin JK, Huster GA: Symptoms of depression in adolescents with epilepsy. J Am Acad Child Adolesc Psychiatr 38:1132-1138, 1999
8. Sheth RD, Stafstrom CE: Intractable pediatric epilepsy: vagal nerve stimulation and the ketogenic diet. Neurol Clin 20:1183-1194, 2002
9. Ben-Menachem E: Vagus nerve stimulation for the treatment of epilepsy. Lancet Neurol 1:477-482, 2002
10. Theodore WH, Fisher RS: Brain stimulation for epilepsy. Lancet Neurol 3:111-118, 2004
11. Zabara J: Inhibition of experimental seizures in canines by repetitive vagal stimulation. Epilepsia 33:1005-1012, 1992
12. Penry JK, Dean JC: Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. Epilepsia 31:S40-S43, 1990 (suppl 2)
13. Uthman BM, Wilder BJ, Penry JK, et al: Treatment of epilepsy by stimulation of the vagus nerve. Neurology 43:1338-1345, 1993
14. Crumrine PK: Vagal nerve stimulation in children. Semin Pediatr Neurol 7:216-223, 2000
15. McLachlan RS: Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia 34:918-923, 1993
16. Henry TR, Bakay RA, Pennell PB, et al: Brain blood-flow alterations induced by therapeutic vagus nerve stimulation in partial epilepsy: II. Prolonged effects at high and low levels of stimulation. Epilepsia 45: 1064-1070, 2004
17. Wheless JW, Baumgartner J, Ghanbari C: Vagus nerve stimulation and the ketogenic diet. Neurol Clin 19:371-407, 2001
18. Helmers SL, Wheless JW, Frost M, et al: Vagus nerve stimulation therapy in pediatric patients with intractable epilepsy: retrospective study. J Child Neurol 16:843-848, 2001
19. Amar AP, Heck CN, Levy ML, et al: An institutional experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique, and outcome. Neurosurgery 43:1265-1276, 1998
20. Amar AP, DeGiorgio CM, Tarver WB, et al: Long-term multicenter experience with vagus nerve stimulation for intractable partial seizures: results of the XE5 trial. Stereotact Funct Neurosurg 73:104-108, 1999
21. Amar AP, Heck CN, DeGiorgio CM, et al: Experience with vagus nerve stimulation for intractable epilepsy: some questions and answers. Neurol Med Chir (Tokyo) 39:489-495, 1999
22. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, et al: Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of the effect on seizures. First International Vagus Nerve Stimulation Study Group. Epilepsia 35:616-626, 1994
23. DeGiorgio CM, Schachter SC, Handforth A, et al: Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. Epilepsia 41:1195-1200, 2000
24. Morris GL, Mueller WM: Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus Nerve Stimulation Study Group E01-E05. Neurology 53:1731-1735, 1999
25. Murphy JV, Wheless JW, Schmoll CM: Left vagal nerve stimulation in six patients with hypothalamic hamartomas. Pediatr Neurol 23:167-168, 2000
26. Wilder RM: The effects of ketonemia on the course of epilepsy. Mayo Clinic Proc 2:307-308, 1921
27. Swink TD, Vining EPG, Freeman JM: The ketogenic diet: 1997. Adv Pediatr 44:297-329, 1997
28. Wheless JW: History and origin of the ketogenic diet, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 31-50
29. Schwartzkroin P: Mechanisms underlying the anti-epileptic efficacy of the ketogenic diet. Epilepsy Res 37:171-180, 1999
30. Stafstrom CE, Bough KJ: The ketogenic diet for the treatment of epilepsy: a challenge for nutritional neuroscientists. Nutr Neurosci 6:67-79, 2003
31. Likhodii SS, Burnham WM: The effects of ketone bodies on neuronal excitability, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 217-228
32. Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004
33. Freeman JM, Freeman JB, Kelly MT: The Ketogenic Diet—A Treatment for Epilepsy (ed 3). New York, NY, Demos Publications, 2000
34. Zupec-Kania B, Werner RR, Zupanc ML: Clinical use of the ketogenic diet: the dietician's role, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 63-81
35. Ballaban-Gil K, Callahan C, O'Dell C, et al: Complications of the ketogenic diet. Epilepsia 39:744-748, 1998
36. Wheless JW: The ketogenic diet: an effective medical therapy with side effects. J Child Neurol 16:633-635, 2001
37. Peterman MG: The ketogenic diet in epilepsy. JAMA 84:1979-1983, 1925
38. Helmholz HF, Keith HM: Eight years' experience with the ketogenic diet in the treatment of epilepsy. JAMA 95:707-709, 1930
39. Livingston S: Dietary treatment of epilepsy, in Livingston S (eds): Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence. Springfield, IL, Charles C. Thomas, 1972, pp 378-405

40. Vining E, Freeman J, Ballaban-Gil K, et al: A multicenter study of the efficacy of the ketogenic diet. Arch Neurol 55:1433-1437, 1998
41. LeFevre F, Aronson N: Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. Pediatrics 105:E46, 2000
42. Magrath G, MacDonald A, Whitehouse W: Dietary practices and use of the ketogenic diet in the UK. Seizure 9:128-130, 2000
43. Coppola G, Veggiotti P, Cusmai R, et al: The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience. Epilepsy Res 48:221-227, 2002
44. Levy R, Cooper P: Ketogenic diet for epilepsy. Cochrane Database Syst Rev 3, 2003
45. Maydell BV, Wyllie E, Akhtar N, et al: Efficacy of the ketogenic diet in focal versus generalized seizures. Pediatr Neurol 25:208-212, 2001
46. Kossoff EH, Pyzik PL, McGrogan JR, et al: Efficacy of the ketogenic diet for infantile spasms. Pediatrics 109:780-783, 2002
47. Nordli DR, Kuroda MM, Carroll J, et al: Experience with the ketogenic diet in infants. Pediatrics 108:129-133, 2001
48. Sirven J, Whedon B, Caplan D, et al: The ketogenic diet for intractable epilepsy in adults: preliminary results. Epilepsia 40:1721-1726, 1999
49. Sperling MR, Nei M: The kerogenic diet in adults, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 103-109
50. Hemingway C, Freeman JM, Pillas DJ, et al: The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively. Pediatrics 108:898-905, 2001
51. Freeman J, Vining E, Pillas D, et al: The efficacy of the ketogenic diet—1998: a prospective evaluation of intervention in 150 children. Pediatrics 102:1358-1363, 1998
52. Pulsifer M, Gordon J, Vining E, et al: Effects of the ketogenic diet on development and behavior: preliminary report of a prospective study. Dev Med Child Neurol 43:301-306, 2001
53. Freeman JM: The ketogenic diet and epilepsy. Nestle Nutrition Workshop Series Clinical and Performance Program 5:307-321, 2001
54. Sokoloff L: Metabolism of ketone bodies by the brain. Ann Rev Med 24:271-279, 1973
55. Nordli DR, DeVivo DC: Effects of the ketogenic diet on cerebral energy metabolism, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 179-184
56. Thio L, Wong M, Yamada K: Ketone bodies do not directly alter excitatory or inhibitory hippocampal transmission. Neurology 54:325-331, 2000
57. Likhodii SS, Serbanescu I, Cortez MA, et al: Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. Ann Neurol 54:219-226, 2003
58. Yudkoff M, Daikhin Y, Nissim I, et al: The ketogenic diet: interactions with brain amino acid handling, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 185-199
59. Sullivan PG, Rippy NA, Dorenbos K, et al: The ketogenic diet increases mitochondrial uncoupling protein levels and activity. Ann Neurol 55: 576-580, 2004
60. Greene AE, Todorova MT, Seyfried TN: Perspectives on the metabolic management of epilepsy through dietary reduction of glucose and elevation of ketone bodies. J Neurochem 86:529-537, 2003
61. Withrow CD: The ketogenic diet: mechanisms of anticonvulsant action, in Glaser GH, Penry JK, Woodbury WM (eds): Antiepileptic Drugs: Mechanisms of Action. New York, NY, Raven Press, 1980, pp 635-642
62. Bough KJ, Eagles DA: A ketogenic diet increases the resistance to pentylenetetrazole-induced seizures in the rat. Epilepsia 40:138-143, 1999
63. Wirrel EC, Darwish HZ, Williams-Dyjur C, et al: Is a fast necessary when initiating the ketogenic diet? J Child Neurol 17:179-182, 2002
64. DeVivo DC, Trifiletti RR, Jacobson RI, et al: Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med 325:703-709, 1991
65. Vining EPG, Pyzik P, McGrogan J, et al: Growth of children on the ketogenic diet. Dev Med Child Neurol 44:796-802, 2002
66. Huttenlocher PR, Wilbourn AJ, Signore JM: Medium-chain triglycerides as a therapy for intractable childhood epilepsy. Neurology 21:1097-1103, 1971
67. Vaisleib II, Buchhalter JR, Zupanc ML: Ketogenic diet: outpatient initiation, without fluid, or caloric restrictions. Pediatr Neurol 31:198-202, 2004
68. Furth SL, Casey JC, Pyzik PL, et al: Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol 15:125-128, 2000
69. Kwiterovich PO, Vining EPG, Pyzik P, et al: Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA 290:912-920, 2003
70. Sutherling JEN, Mele-Hayes D: How to maintain and support a ketogenic diet program: a nursing perspective, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 83-94
71. Stafstrom CE, Holmes GL: Dietary treatments for epilepsy other than the ketogenic diet, in Stafstrom CE, Rho JM (eds): Epilepsy and the Ketogenic Diet. Totowa, NJ, Humana Press, 2004, pp 161-175
72. Kossoff EH: More fat and fewer seizures: dietary therapies for epilepsy. Lancet Neurol 3:415-420, 2004
73. Atkins RC: Dr. Atkins' New Diet Revolution. New York, NY, Avon, 2002
74. Kossoff EH, Krauss GL, McGrogan JR, et al: Efficacy of the Atkins diet as a therapy for intractable epilepsy. Neurology 61:1789-1791, 2003
75. Baxter P: Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the U.K. Arch Dis Child 81:431-433, 1999
76. Baxter P: Pyridoxine-dependent seizures: a clinical and biochemical conundrum. Biochim Biophys Acta 1647:36-41, 2003
77. Gospe SM: Pyridoxine-dependent seizures: findings from recent studies pose new questions. Pediatr Neurol 26:181-185, 2002
78. Baxter P, Griffiths P, Kelly T, et al: Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. Dev Med Child Neurol 38:998-1006, 1996
79. Sterman MB: Studies of EEG biofeedback training in man and cats, in Highlights of 17th Annual Conference: VA Cooperative Studies in Mental Health and Behavioral Sciences. 1972, pp 50-60
80. Sterman MB: Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. Clin Electroencephalogr 31:45-55, 2000
81. Sterman MB, Friar L: Suppression of seizures in epileptics following sensorimotor EEG feedback training. Electroencephalogr Clin Neurophysiol 33:89-95, 1972
82. Andrews DJ, Schonfeld WH: Predictive factors for controlling seizures using a behavioural approach. Seizure 1:111-116, 1992
83. Lubar JF, Shabsin HS, Natelson SE, et al: EEG operant conditioning in intractable epilepsies. Arch Neurol 38:700-704, 1981
84. Kaplan BJ: Biofeedback in epileptics: equivocal relationship of reinforced EEG frequency to seizure reduction. Epilepsia 16:477-485, 1975
85. Gastaut H: Comments on "Biofeedback in epileptics: equivocal relationship of reinforced EEG frequency to seizure reduction." Epilepsia 16:487-488, 1975
86. Rockstroh B, Elbert T, Birbaumer N, et al: Cortical self-regulation in patients with epilepsies. Epilepsy Res 14:63-72, 1993
87. Kotchoubey B, Strehl U, Holzapel S, et al: Negative potential shifts and the prediction of the outcome of neurofeedback therapy in epilepsy. Clin Neurophysiol 110:683-686, 1999
88. Kotchoubey B, Strehl U, Uhlmann C, et al: Modification of slow cortical potentials in patients with refractory epilepsy: a controlled outcome study. Epilepsia 42:406-416, 2001
89. Nagai Y, Goldstein LH, Critchley HD, et al: Influence of sympathetic autonomic arousal on cortical arousal: implications for a therapeutic behavioural intervention in epilepsy. Epilepsy Res 58:185-193, 2004
90. Nagai Y, Goldstein LH, Fenwick PB, et al: Clinical efficacy of galvanic skin response biofeedback training in reducing seizures in adult epilepsy: a preliminary randomized controlled study. Epilepsy Behav 5:216-223, 2004
91. Ramaratnam S, Baker GA, Goldstein L: Psychological treatments for epilepsy. Cochrane Database Syst Rev 4:CD002029, 2003