Role of some nutritional complements and biological supplements in the management of epilepsy

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ABSTRACT

Various dietary components, biological supplements might influence the incidence or management of epilepsy. Some studies reported that the supplementation with individual nutrients reduced seizure occurrence or improved other facets of health in epileptic patients. The beneficial dietary involvement identifying and avoiding allergenic foods, and avoiding suspected causing agents such as alcohol, aspartame, and monosodium glutamate. The Atkins diet (very low in carbohydrates) is a less preventive type diet that may be effective in some cases. Nutrients that may lessen seizure occurrence include vitamin B<sub>6</sub>, magnesium, vitamin E, manganese, taurine, dimethylglycine, and omega-3 fatty acids. Use of thiamine or vitamin B<sub>1</sub> may improve cognitive function in epileptic patients. Supplementation with folic acid, vitamin B<sub>6</sub>, biotin or viatamine H, vitamin D, and L-carnitine may be needed to prevent or treat deficiencies resulting from the use of antiepileptic drugs. Vitamin K<sub>1</sub> is recommended near the end of pregnancy for women taking antiepileptic drugs. Melatonin may reduce seizure occurrence in some cases, and progesterone may be useful for women with cyclic exacerbations of seizures. In the majority of cases, nutritional therapy is not a substitute for antiepileptic drugs. In some cases, depending on the effectiveness of the involvement, dosage reduction or discontinuation of drugs may be possible. However, nutrient supplementation may be necessary to prevent or reverse the effects of certain deficiencies that regularly result from the use of antiepileptic drugs.

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Capsule Summary: The dietary and nutritional supplements are considerations in patients with epilepsy and also the relationship among foods, dietary elements, and seizures.


INTRODUCTION

What Causes Epilepsy: Almost 1% of people will develop epilepsy in their lifetime. Epilepsy can develop in any person at any age. New cases of epilepsy are common among children, especially during the first year. The rate of new cases slowly declines until about age 10 and then become stable. After age 60 year, the rate starts to increase again. The reasons of epilepsy can be divided into two groups, chemical imbalances and injuries in the brain. Anything that injures the brain can lead to seizures. But over half the cases no cause can be identified. The type of injury that can lead to a seizure is age-dependent. Seizures in children often are caused by birth traumas, infections, like
meningitis, congenital abnormalities, high fevers. Seizures in the middle years mainly are caused by head injuries, infections, alcohol, CNS stimulant drugs or drugs side effects. In the elderly, brain tumors and strokes cause a high proportion of seizures. Not all seizures result from an injury in the brain. Chemical imbalances also can cause seizures. General chemical imbalances that can produce seizures include drugs like alcohol, cocaine and others, low blood sugar, low oxygen, low blood sodium or low blood calcium level. Kidney failure or liver failure can also produce seizures. These disorders and injuries can explain various cases of epilepsy, often the cause of epilepsy remains idiopathic. Fortunately, we do not need to know the cause to treat the seizures. Researchers increasingly recognize the importance of genetic factors in the origin of epilepsy. Genetics or heredity is most relevant to generalized seizures, including petitmal, grandmal and myoclonic seizures. Typically, epilepsy develops because of multiple gene abnormalities or because of a gene abnormality in concert with an environmental trigger. If the mother has a generalized type of epilepsy, then the child’s chance of having epilepsy may be as high as 5-20%. But if a parent has epilepsy due to a brain injury, the child’s chance of having epilepsy is only about 5% (Asadi-Pooya et al., 2008).

Diet is a basic aspect of human life and patients with epilepsy often report or ask if foods are related to their illness. While foods are normally considered undesired provoking agents for seizures, dietary and nutritional involvements are sometimes considered useful and even therapeutic. As antiepileptic drugs (AEDs) inadequately control seizures in many patients, some researchers have attempted nutritional supplementation in an effort to reduce seizure incidence or improve other aspects of health in epileptic patients. Nutrient supplementation may also be necessary to prevent the effects of certain deficiencies that might result from the use of AEDs. However, the potential benefits of nutrient supplementation in patients with epilepsy must be weighed against reports that large doses of certain nutrients (e.g., vitamin B6 and folic acid) can interfere with the effects of some AEDs (Gaby, 2007). The ketogenic diet, which is the most accepted dietary treatment for epilepsy (Asadi-Pooya et al., 2008). There are several reports suggested that certain foods might trigger seizures. However, the presented data are limited and controlled studies are lacking.

**Nutrition and Epilepsy**

It is essential that people with epilepsy follow a nutritious, well balanced diet. Good nutritional habits and healthy lifestyle are important in obtaining optimal seizure control. However, no special diet is prescribed for epilepsy itself. To avoid dietary deficiencies, ensure proper intake of nutrients through a diet containing adequate folic acid (found in raw and slightly cooked fruits and vegetables), calcium and magnesium (found mainly in dairy products), vitamin (Vit) B12 (animal and dairy products), and Vit K (leafy green vegetables and cereal grains). Vitamin D is found in fish oils and flesh, supplemented milk, and is made in the body in response to sunlight. If you have some other condition in addition to epilepsy, that requires a special diet (diabetes, for example), it is important that you follow the diet needed for that disorder. The medicines that control seizures may interfere with the body’s ability to use certain nutrients including Vit D, Vit K, calcium, magnesium, manganese and folic acid. While this problem is in most people who take medications, it is usually mild and causes no harm. Those most susceptible to Vit deficiencies include, people on large doses of medication or multiple drugs; the elderly; growing children; pregnant women; alcohol abusers; and those who follow poor dietary habits. If the body is depleted of these substances (Ca and Mg), convulsions may occur. However, unless some other disease that affects these substances, will not have problems with them if eat a balanced diet (Tyagi and Delanty, 2003; Volpe et al., 2007; Yuen et al., 2005).

The use of antiepileptic drugs (AEDs) may have an adverse effect on Vitamins. Problems can generally be avoided with a proper diet. However, in rare, more serious problems may arise. For example, anemia can result from severe folic acid deficiency. Weak bones are related to inadequate amounts of vit D. Vitamin supplements can be prescribed as necessary. Extreme, self-prescribed “megavitamin” therapy will do no good and could be harmful. For example, excessive folic acid intake may actually decrease seizure control. “Ketogenic Diet” is a special, high fat diet approximates the metabolic circumstances of starvation. This state (in which the excessive fats produce chemicals called ketones) has been effective in controlling seizures in young children when AEDs proved ineffective. The diet seldom works in children over 16 years of age and is not effective for all seizure types. The majority of caloric intake is obtained from fatty foods. It is quite unpalatable and difficult to maintain. Overall, it is reserved for children with epilepsy who are unresponsive to AEDs. Another version of the diet-the medical chain triglyceride (MCT) diet (Tyagi and Delanty. 2003; Volpe et al., 2007; Yuen et al., 2005), in extreme cases, nevertheless, blood sugar level should be steady and moderate for people with epilepsy. Sweets, caffeine and alcohol all cause blood sugar levels to fluctuate and should be avoided. High fibre-whole wheat toast or a bran muffin—helps control fluctuations of blood sugar. Protein is also important in the metabolism of certain brain chemicals and hormones. Some individuals are sensitive to missing meals. If meals are missed or delayed, seizure frequency may increase. Therefore, regular meals and balanced diets are recommended. Substances (caffeine, alcohol or smoking) are best considered drugs rather than part of the diet. Like other drugs they can do harm, particularly if taken too often or in large amounts. Alcohol is of special concern. When used frequently or in large amounts, alcohol may interfere with the AEDs and may lower seizure threshold. While smoking can leads to seize. Food allergies do not cause epilepsy. They may aggravate a pre-existing seizure problem (Tyagi and Delanty. 2003; Volpe et al., 2007; Yuen et al., 2005). The induction of seizures and status epilepticus with a high mortality rate were reported due to star fruit intoxication in patients with chronic renal disease. An excitatory neurotoxin from star fruit has been implicated although the exact nature of this toxic substance has not been identified. The mortality rate after star fruit intoxication ranges as high as 20-40%. As no effective treatment has been established, star fruit consumption should be avoided in patients with chronic renal disease, especially in the elderly (Tsai et al., 2005).

**Amino acids**
Studies have reported the reduction of seizure threshold in rats administered with excess dietary amino acids and the induction of convulsions by monosodium glutamate. A report indicated ingestion of monosodium glutamate appeared to trigger or exacerbate seizures in a child with Lennox–Gastaut syndrome (Shovic et al., 1997), though this had several limitations (Auer, 1998).

**Aspartame**: Aspartame may provoke seizures, particularly in for phenyl ketonuria (PKU) (Camfield et al., 1992; Tyagi & Delanty, 2003; Rowan et al., 1995). Patients whose seizures were allegedly related to aspartame, none experienced seizure exacerbation with aspartame (50 mg/kg), a dose that is much higher than expected in a regular diet. Aspartame might undergo chemical changes on exposure to high temperatures or after storage (Gaby, 2007). It should be mentioned that either anecdotal or animal studies; proconvulsive effects of foods have never been proved in randomized, controlled clinical trials in humans. Whether other, more commonly consumed edibles bring on seizures is even less certain (Asadi-Pooya et al., 2008).

**Caffeine**

There are reports of increased seizure frequency in patients with epilepsy due to ingestion of foods or beverages containing central nervous system (CNS) stimulants (e.g., caffeine). Caffeine blocks adenosine receptors and act as CNS stimulant. This might be responsible for increased neuronal repetitive firing and seizures (Kaufman & Sachdeo, 2003; Bonilha and Li, 2004). However, caffeine has differential actions on different brain areas. It has inhibitory effects on the medial thalamus and excitatory effects on brain stem reticular formation (Chou et al., 1980). Its effects with regard to triggering seizures, caffeine can induce hepatic CYP-1A enzymes, which are involved in the metabolism of many drugs including carbamazepine (Goasduff et al., 1996). This might lower serum drug levels and thereby increase the likelihood of having a seizure. Due to the habit of coffee and tea drinking, further attention should be paid to the potential effects of caffeine in seizure control, but at the moment, there is not enough evidence to suggest that reduction of the daily intake of coffee or tea might help the treatment of patients with refractory seizures. On the other hand, regardless of its effects on seizures, there is growing evidence that caffeine, like certain AEDs, can adversely affect bone density (Tsuang et al., 2006; Gissel et al., 2007; Rapuri et al., 2007). It was reported that women with caffeine intakes >300 mg/day had higher bone loss, possibly due to decrease in Vit D receptor protein expression (Rapuri et al., 2007). Caffeine consumption was reported to decrease bone mineral density, increase the risk of hip fracture, and negatively influence calcium retention, possibly due to deleterious effects on the osteoblasts viability, which may enhance the rate of osteoblast apoptosis (Tsuang et al., 2006). The effects of caffeine and AEDs on bone metabolism and density are additive has not been studied, but it may be prudent that patients with epilepsy, particularly those individuals with other risk factors for or evidence of decreased bone mineral density, avoid excessive intake of caffeine (Asadi-Pooya et al., 2008).

**Carnitine**: Treatment of children with valproic acid, particularly in combination with other antiepileptic drugs (AEDs), reduced total and free carnitine concentrations and increased plasma ammonia concentrations (a sign of carnitine deficiency). Carnitine levels in patients taking AEDs other than valproic acid were normal (Verrotti et al., 1999; Opala, et al., 1991). L-carnitine supplementation is indicated for patients with symptomatic valproic acid-associated hyper-ammonemia, multiple risk factors for valproic acid hepatotoxicity, or renal-associated syndromes; infants and young children taking valproic acid; epileptic patients using the ketogenic diet who have low serum carnitine levels; patients receiving dialysis; and premature infants receiving total parenteral nutrition. The recommended an oral L-carnitine dosage of 100 mg/kg/day, to a maximum of 2 g/day. Intravenous L-carnitine was suggested for valproic acid-induced hepatotoxicity and other acute metabolic crises associated with carnitine deficiency.

In a study, few valproate-treated children developed clinical symptoms (e.g., fatigue) and biochemical evidence of carnitine deficiency (Van Wouwe, 1995). In some others, an asymptomatic biochemical deficiency was found. If a patient complains of fatigue during prolonged valproic acid treatment, advise carnitine supplementation. In addition, some data supported that the hypothesis that l-carnitine treatment significantly enhances the survival of patients with severe valproate induced hepatotoxicity (Verrotti et al., 2002). Oral L-carnitine supplementation is also suggested for infants and young children receiving valproate, especially those with a complex neurological disorder who are receiving multiple AEDs, patients who have multiple risk factors for hepatotoxicity (neurological impairments, poor nutrition, failure to thrive, chronic illness, receiving multiple AEDs), and those receiving dialysis (De Vivo et al., 1998).

**Food allergy**

The convulsions might be associated with allergy (certain foods or allergens) (Egger et al., 1989; Pelliccia et al., 1999; Frediani et al., 2001), but others have refuted this hypothesis (Castaneda et al., 1998; Asadi-Pooya & Ghetmiri, 2007). So far, the evidence with regard to the relationship between epilepsy and allergic disorders is preliminary and more work is needed. However, if certain foods are reliably associated with seizures in an individual patient, avoiding the offending food might be tried, but proper nutritional intake should not be compromised. Specific foods were implicated in epilepsy causation; the avoidance of symptom-evoking foods resulted in a reduction in seizure frequency or elimination of seizures (Reichelt et al., 1990; Schmidt et al., 1981). In a study of children with epilepsy, identification and avoidance of allergenic foods was frequently successful for patients who had other symptoms suggestive of allergy, but not for children who had epilepsy alone. For four weeks, children with epilepsy underwent an elimination diet consisting of lamb, chicken, potato, rice, banana, apple, cabbage, sprouts, cauliflower, broccoli, cucumber, celery, carrots, parsnips, water, salt, pepper, pure herbs, calcium, and vitamins. Some children who had epilepsy alone, none improved. The other children with epilepsy also had recurrent migraines, abdominal symptoms, or hyperkinetic behavior. Of those
children. 56 percent stopped having seizures and an additional 24 percent had fewer seizures during diet therapy (total 80 percent with complete or partial resolution of seizures). Headaches, abdominal pains, and hyperkinetic behavior resolved in all patients whose seizures resolved, as well as in some patients who continued to have seizures. Symptoms were evoked by different foods, and seizures occurred after ingestion of different foods. Most children reacted to several foods. Both generalized epilepsy (myoclonic seizures and petit mal) and partial epilepsy improved on the diet (Egger et al., 1989). The prevalence of celiac disease has been found to be higher in patients with epilepsy than in controls (Cronin et al., 1998). Seizures have improved in patients with celiac disease who consumed a gluten-free diet (Pratesi et al., 2003); but only when the diet was started soon after the onset of epilepsy (Gobbi et al., 1992). Most epileptic patients with celiac disease did not have gastrointestinal symptoms at the time of presentation, so testing for celiac disease should be considered even in the absence of such symptoms. Some epileptic patients and celiac disease have also been found to have cerebral calcifications, (Hernandez et al., 1998; Piattella et al., 1993; Ventura et al., 1991).

Celiac disease
Celiac disease is a multisystem autoimmune disorder triggered by the ingestion of gluten in genetically susceptible individuals. The occurrence of celiac disease has been found to be higher in epileptic patients (Cronin et al., 1998). In a report of patients with celiac disease, epilepsy and cerebral calcifications (Gobbi et al., 1992), seizures were poorly responsive to AEDs. Gluten-free diet usefully affected the course of epilepsy only when started soon after epilepsy onset. High index of disbelief is essential for the diagnosis of celiac disease and search for this disease is recommended in patients with childhood partial epilepsy with occipital paroxysms (Labate et al., 2001). Serum antibodies to tissue transglutaminase are reliable markers that may be used for celiac disease screening (De Lecea et al., 1996).

Food and drug interactions
Food–drug interaction (FDI) is an important. Foods may alter the effects of drugs by interfering with pharmacokinetic processes, like absorption and elimination. In a study, it was observed that grapefruit juice significantly increased carbamazepine serum level (Garg et al., 1998). Grapefruit juice increases the bioavailability of carbamazepine by inhibiting CYP3A enzymes in gut wall and in the liver. A number of environmental agents like smoking, alcohol consumption, and dietary elements may induce hepatic drug-metabolizing enzymes, which may have significant effects on the pharmacokinetics of certain drugs including some AEDs (Hewitt et al., 2007). Few studies have showed the effects of various foods on different hepatic enzymes (Hidaka et al., 2004, 2005; Kim et al., 2006; Hewitt et al., 2007). These foods might potentially affect the plasma levels of AEDs metabolized by hepatic enzymes, which may lead to either drug toxicity or inefficacy (Patsalos et al., 2002; Anderson, 2004). Future studies investigating the interactions between foods and cytochrome P450 enzymes are necessary to determine whether inhibition or induction of these enzymes activity by foods is clinically relevant. However, several patients in which grapefruit juice appears to have produced clinical toxicity by increasing serum drug levels.

Other nutrients
Manganese deficiency was reported in patients with epilepsy, though it does not appear to correlate with seizure frequency, types, dose, or plasma levels of AEDs (Carl et al., 1986). The ω-3 fatty acids increase seizure thresholds and lower inflammatory mediators, which are increased in epileptic patients. Linolenic acid prevents kainate-induced seizures and neuronal death and has neuro-protective effects (Lauritzen et al., 2000). Supplementation with fish oil, providing ω-3 fatty acids, reduced seizure frequency during the first 6 weeks of treatment, but the beneficial effect was not sustained there after (Yuen et al., 2005). Large amounts of ginkgo nuts and the consumption of star fruit in patients with chronic renal disease may produce seizures. In patients (mainly children) with occipital lobe epilepsy, it is recommended to screen for celiac disease. While pyridoxine, folic acid and biotin supplemements are necessary in patients with cerebral folate deficiency or biotinidase deficiency, respectively and to control the seizures. Carnitine supplementation might be helpful in some patients who are taking valproate and low dose of folate supplementation may prevent carbamazepine-induced leukopenia or anemia. The use of high dose of folic acid supplements in women with epilepsy before conception and during pregnancy, supplementation with Vit D in patients taking enzyme-inducing AEDs and valproate, and finally Vit K in pregnant women taking AEDs and their newborns are recommended. The relation between other nutrients (Vit E and ω-3 fatty acids and seizures) should be investigated. It should be mentioned that a food–drug interaction has been observed between grapefruit juice and carbamazepine. The interactions between foods and cytochrome P450 enzymes are still needed to determine whether inhibition or induction of these enzymes activity is clinically relevant. There are many different types of epilepsy, a nutritional intervention that is helpful for one syndrome or seizure type might not be beneficial for another. Unnecessary and excessive vitamin and mineral supplementation may actually be harmful. For many people with epilepsy a healthy, balanced diet is the best, but many patients have nutritional deficiencies. In a study, at least 30% of children with intractable epilepsy had intakes below the recommended dietary allowance for Vit D, E, and K, folate, calcium, and linoleic acid (Volpe et al., 2007). Caring for patients with epilepsy, especially children with intractable epilepsy should be aware of these nutritional recommendations and educate families to provide an adequate diet and/or consider vitamin/mineral supplementation. Given the high probability of any patient not eating a well-balanced diet, routine vitamin supplementation with modest doses can be considered reasonable (Asadi-Pooya et al., 2008).

Dietary Factors

Hypoglycemia
Seizures are a known sign of hypoglycemia (Monami et al., 2005; Liu et al.1588). In patients with epilepsy, hypoglycemia might decrease the threshold for seizure development. In a study of patients with epilepsy, 56.4 percent were found to have a subnormal fasting blood glucose concentration. In addition,
transient EEG abnormalities have been observed in some patients during a glucose tolerance test. These abnormalities occurred, not when the blood glucose level was at its lowest point, but at a time that insulin levels would have been expected to be elevated (Hudspeth et al., 1981). These EEG changes were hypothesized to result from insulin-induced transport of water and electrolytes into the brain, leading to cerebral hyperosmolality. These results raise the possibility that hyper-insulinemia could trigger seizures in epileptic patients (Crayton et al., 1981; Asif. 2014; Asif. 2013a). Thus, hypoglycemia and hyper-insulinemia might each contribute to the pathogenesis of epilepsy. Patients with epilepsy who have evidence of these abnormalities might benefit from nutritional interventions, such as avoiding refined sugar, caffeine, alcohol; eating frequently; consuming adequate amounts of protein; and supplementing with chromium, other trace minerals, magnesium and B vitamins.

Dietary provocative factors
In some cases, epileptic seizures have been triggered by excessive alcohol intake (Wolf, and OkuJava. 1999). The reports indicate ingestion of monosodium glutamate appeared to trigger or exacerbate seizures in children (Shovic et al., 1997). Grand mal seizures have occurred after consumption of aspartame by people who had no prior history of epilepsy (Wurtman. 1985; Walton.1986). Ingestion of a drink containing aspartame (40 mg/kg body weight) also exacerbated EEG spike-wave discharges in children with a history of absence seizures (Camfield et al., 1992). However, administration of aspartame (34 mg/kg/day for two weeks or a single dose of 50 mg/kg) did not provoke seizures in patients with epilepsy or in people who reported a history of aspartame-induced seizures (Shaywitz et al., 1994; Rowan, et al., 1995). As aspartame is undergoes chemical changes on exposure to high temperatures or after storage for more than two months, these degradation products may be partly responsible for the reported adverse effects of aspartame (Roberts. 1995). Based on the evidence, aspartame should be considered a potential trigger for seizures and should be excluded during an elimination diet.

Ketogenic Diet
The ketogenic diet has been used to control seizures in children who do not respond to antiepileptic drugs (Kinsman, et al., 1992; Hemingway et al., 2001; Vining. 1999; Gasch. 1990; Tallian et al., 1998; Kaytal et al., 2000; Hassan, et al., 1999; Freeman, et al., 1998; Vining, et al., 1998). The diet is calorie-restricted and provides a ratio of fat to (carbohydrate and protein) ranging from 2.1 to 5.1. The proportion of total energy derived from fat ranges from 82-92 percent. Consuming a ketogenic diet produces a state of ketosis, which helps control seizures. Fluid intake is restricted to maintain urine specific gravity at 1.020-1.025, since fluid intake dilutes blood ketones. In other studies, 40-70 percent of patients following the diet experienced at least a 50-percent reduction in seizure frequency, and 10-33 percent became seizure-free. In many cases, drugs could be discontinued or the dosages decreased. Two children with acquired epileptic aphasia were also successfully treated with this diet (Bergqvist, and Brooks-Kayal. 1997). Myoclonic epilepsy responds best to the ketogenic diet. However, other study found that the response to the diet did not vary significantly according to seizure type (Vining. 1999). The diet is most effective in children ages 2-5 years, although patients of other ages have also benefited (Gasch. 1990). However, some investigators have found that it is not necessary to begin the diet with a fast. The ketogenic diet is usually followed for about two years, after which the proportion of fat is reduced gradually over 6-9 months to that of a regular diet. After a patient has been on the diet for two years, seizures are less likely to recur on resumption of a normal diet. The diet regimen is repeated if seizures recur. There are some drawbacks to the ketogenic diet. Supplementation with multivitamins, calcium, and iron is necessary to prevent nutritional deficiencies. The ketogenic diet is unpalatable and is difficult for parents to administer.

While most ketogenic diet studies have been conducted in children and also it effect in adults with refractory epilepsy. At eight months of follow-up, some patients had a 90-percent reduction in seizure frequency, some patients had a 50- to 89-percent decrease, and few patients had a less-than-50-percent decrease. All types of seizures responded to the diet. Main adverse effects included constipation, menstrual irregularities, and increases in triglyceride levels and cholesterol/HDL ratios (Sirven, et al., 1999). The triglycerides of octanoic and decanoic acids (medium-chain triglycerides MCTs) are more ketogenic than long-chain triglycerides present in dietary fats. Diets containing large proportions of MCTs are more palatable, better tolerated, and require less carbohydrate and protein restriction than standard ketogenic diets. The MCT ketogenic diet, which provides 50-70 percent of total energy in the form of MCTs, has been used as an alternative to the classic ketogenic diet (Trauner. 1985). Adherence to this diet resulted in improvement or complete control of seizures in 44 percent of children with drug-resistant epilepsy (Sills, et al.,1986). Children who have had a positive response to this diet may be able to taper off the diet after 3-4 years without experiencing a recurrence of seizures. While the MCT diet is frequently well tolerated, some patients abandon it because of gastrointestinal intolerance (Asif. 2013b; Asif. 2013c).

Ketogenic diet adverse effects
The ketogenic diet has caused a number of adverse effects with some serious. Initiation of the diet can result in vomiting, hypoglycemia, or dehydration. In a study, serious adverse events (hypo-proteinemia, Fanconi’s renal tubular acidosis, or marked abnormalities on liver function tests) occurred in some children on a ketogenic diet (Ballaban-Gil, et al., 1998). Other potential side effects include increased bruising or other minor bleeding (prolonged bleeding time), constipation, and diarrhea (Berry-Kravis, at al., 2001; Edelstein, and Chisholm. 1996). Long-term problems include moderate growth retardation, renal stones (5-8%), gallstones, acidosis or metabolic problems, recurrent infections, hypercholesterolemia, hyperuricemia, vitamin deficiency and feeding problems. Prolonged ketosis may raise the serum level of phenobarbitone, which can result in alopecia, renal stones, and growth retardation. The ketogenic diet and antiepileptic drugs (AEDs) both have an adverse effect on bone density, which can be partially reversed with Vit D supplementation. Carnitine deficiency may also occur with the ketogenic diet, particularly in patients taking valproic acid. L-carnitine supplementation is recommended for patients who have...
low serum carnitine levels (De Vivo, et al., 1998). Patients on the ketogenic diet must be monitored closely.

**Atkins diet:** The Atkins diet is a low-carbohydrate, high fat diet used for weight reduction. Like the ketogenic diet, the Atkins diet can induce a state of ketosis, but it has fewer restrictions on calories and protein. The Atkins diet does not require fluid restriction. The Atkins diet may be an effective alternative to the ketogenic diet in some children with intractable epilepsy. The children (3-18 years) with intractable epilepsy, with at least three seizures per week, who had been treated with at least two antiepileptic drugs (AEDs), followed a modified Atkins diet over a six-month period. Carbohydrates were limited to 10 g/day for the first month and consumption of fats was encouraged. All children received vitamin and calcium supplements. At six months, most patients (65%) had more than 50-percent improvement and some patients (35%) had more than 90-percent improvement (few were seizure-free). Small increases were seen in serum cholesterol and blood urea nitrogen levels (Kossoff, et al., 2006). Adults with epilepsy showed no improvement on the Atkins diet (Kossoff et al., 2003).

**Nutritional Supplements**

**Taurine**

Taurine acts as a modulator of membrane excitability in the CNS by inhibiting the release of other neurotransmitters and decreasing mitochondrial release of calcium. Taurine concentrations was found to be elevated in serum, but decreased in the brain, in some epileptic patients. In contrast, serum concentrations of most other amino acids were lower in epileptic patients than in healthy humans. Taurine partially corrected these low serum amino acid concentrations (Goodman et al., 1980). Taurine has been administered at a wide range of doses (200 mg/day to 21 g/day) for varying periods of time to patients with severe, intractable epilepsy. A significant reduction in seizure frequency was observed, whereas no benefit was seen in others. Taurine was effective against partial epilepsy but had little effect on generalized epilepsy. The beneficial effects of taurine frequently diminished or disappeared after few weeks. The loss of efficacy is that high-dose taurine caused amino acid imbalances, as suggested by the appearance of generalized amino aciduria in a patient during treatment daily with 2.0-2.5 g taurine. The optimal dose of taurine to treat epilepsy might be in the range of 100-500 mg/day, and in one report a loss of antiepileptic activity was seen in some patients when the dose was increased above 1.5 g/day. While additional studies are needed to determine taurine’s optimal dosage range to produce long-lasting improvement of epilepsy.

**Dimethylglycine**

Dimethylglycine, a metabolite of betaine, demonstrated antiepileptic activity in mice (Freed, 1985), but not in another study (Haidukewych and Rodin. 1984). A mentally handicapped man with mixed complex, partial, and grand mal seizures had been having 16-18 generalized seizures per week, despite therapeutic levels of phenobarbital and carbamazepine. He taken 90 mg dimethyl glycine twice daily because of a suggestion it might improve his stamina. Within one week his seizure frequency dropped to three per week. Two attempts to withdraw dimethyl-glycine resulted in a dramatic increase in seizures (Roach and Carlin. 1982). Administration of dimethylglycine to epileptic patients in doses of 300-810 mg/day for up to 30 days did not produce any improvement (Roach and Gibson. 1983; Gascon et al., 1989). One patient who benefited from dimethylglycine may have had an isolated metabolic defect that was overcome by treatment with this compound.

**Essential Fatty Acids**

Severely mentally handicapped patients (ages 12-26 years) with more than 3-4 grand mal seizures per month received a daily supplement providing 900 mg eicosapentaenoic acid (EPA), 2.3 g docosahexaenoic acid (DHA), and 50 mg α-linolenic acid. All patients experienced a marked reduction in both frequency and severity of grand mal seizures (Schlanger et al., 2002). In a study that adults, supplementation with fish oil (providing 1 g/day EPA and 0.7 g/day DHA) reduced seizure frequency during the first six weeks of treatment, but the beneficial effect was not sustained thereafter (Yuen, et al., 2005). In contrast to the possible beneficial effect of ω-3 fatty acids, the ω-6 fatty acids in evening primrose oil may have deleterious effects in some epileptic patients. Several reported, in which administration of evening primrose oil appeared to exacerbate or unmask temporal lobe epilepsy (Vaddadi et al., 1986; Vaddadi. 1981; Holman and Bell. 1983).

**Hormones**

**Melatonin**

In a study, 3 mg melatonin was given each night for three months to six children (ages 2-15 years) with severe, intractable seizures. The mean seizure frequency decreased from 3.6 per day at baseline to 1.5 per day during treatment (58% reduction). Melatonin has also been used in doses of 2-10 mg before bedtime to treat sleep disturbances in children with epilepsy. Melatonin treatment was associated with an increase in seizure frequency in some patients and a decrease in others (Jones et al., 2005; Sheldon. 1998; Fauteck et al., 1999). Because melatonin appears to have unpredictable effects on seizure frequency, it should be used with caution in patients with epilepsy.

**Progesterone**

Progesterone may be beneficial for women who have seizure exacerbations at specific times during the menstrual cycle. Women with cyclic exacerbation of complex partial or secondary generalized motor seizures of temporal origin received progesterone lozenges (200 mg 3 times/day). Women with perimenstrual exacerbations received treatment on days 23 to 25 of each cycle; women who had exacerbations during the entire luteal phase were treated from days 15 to 25 of each menstrual cycle. In both groups of women, progesterone was tapered after day 25 and discontinued by day 28. Progesterone was well tolerated by 23 of the 25 women. Most women experienced a reduced seizure frequency during the three-month treatment period. The average frequency of complex partial seizures declined and the frequency of secondary generalized motor seizures declined (Herzog. 1995).
DISCUSSION

Epilepsy is a disorder of brain electrical activity that results in recurrent seizures. The type of seizure depends on the portion of the brain affected. While there are many different causes of seizures, including brain tumor, injury, stroke, and alcohol withdrawal etc. Conventional treatment of epilepsy consists primarily of antiepileptic drugs (AEDs). Although these drugs often control or reduce the frequency of seizures, some patients show little or no improvement. A number of dietary modifications, nutritional supplements, and hormones have been found to be beneficial for some epileptic patients. Potentially useful dietary interferences include measures to stabilize blood glucose levels, avoidance of allergenic foods, and avoidance of inciting agents (ethanol and aspartame). The ketogenic diet is successful for many patients, but because of its highly restrictive nature and potential to cause significant adverse effects, its use is restricted to severe cases that fail to respond to other treatments. A less restrictive version of the ketogenic diet, the Atkins diet, has shown promise and deserves further study (Gaby. 2007).

Several different nutrients or hormones may also be beneficial in selected patients with epilepsy. The nutritional factors are involved in the regulation of electrical activity in the brain is indicated by the fact that severe deficiency of thiamine, magnesium, or Vit B6 can cause seizures. A subnormal concentration of each of these nutrients has been found to be common in epileptic patients. While the severity of these deficiencies is probably not great enough in most cases to cause seizures in otherwise healthy people, marginal status with respect to any of these nutrients could conceivably exacerbate a seizure disorder. Some epileptic patients might have a higher-than-normal requirement for one or more nutrients that play a role in brain electrical activity. In the case of Vit B6-dependent epilepsy, a condition in which intractable seizures can be completely controlled by administration of large doses of Vit B6. While mildly or moderately increased requirements for Vit B6 or other nutrients may not by themselves be sufficient to cause seizures, a failure to meet these increased requirements could aggravate an existing seizure disorder. Supplementation with individual nutrients reduced seizure frequency or improved other aspects of health in patients with epilepsy. Combinations of nutrients might be more effective than supplementing with a single nutrient, but that possibility has largely been unexplored. Nutrient supplementation may also be necessary to prevent or reverse the effects of certain deficiencies that frequently result from the use of AEDs. The potential benefits of nutrient supplementation in patients with epilepsy must be weighed against reports that large doses of certain nutrients (Vit B6 and folic acid) can interfere with the effects of AEDs. Because there are many different types of epilepsy, a nutritional intervention that is helpful for one patient may not be beneficial for another. So it is difficult to generalize results. Nevertheless, natural approaches to the treatment of epilepsy show promise and should be considered as part of the treatment of epilepsy (Asif. 2013a; Gaby. 2007).

CONCLUSIONS

Various different dietary modifications, nutritional supplements, and hormones may help prevent seizures or improve other aspects of health in patients with epilepsy. Supplementation with specific nutrients should also be considered for the prevention and treatment of nutritional deficiencies resulting from anti-epileptic drugs (AEDs). The nutritional therapy is not a substitute for AEDs. However, in selected cases, depending on the effectiveness of the interventions, dosage reductions or discontinuation of drugs may be possible. Because much of the research on epilepsy treatment with diet, nutrients, and hormones is preliminary, there are few clear guidelines on when and how to use the various interventions are described. However, consideration of basic aspects of nutrition and metabolism should aid the clinician and making rational clinical decisions. For example, hypoglycemia should be considered a potential triggering factor in patients who develop seizures in the late morning or late afternoon or when a meal is missed. Food allergy might be a contributing factor in epileptic patients who have other manifestations of possible allergy, like migraines, asthma, or history of recurrent ear infections in childhood. A trial of manganese supplementation would appropriate for patients with low whole-blood manganese concentrations. A trial with Vit E would seem reasonable for many patients with epilepsy, particularly children. Supplementation with magnesium (200-600 mg per day) and modest doses of Vit B6 (10 mg per day) for nutritional support would also be reasonable for many patients, large proportion of the population has suboptimal intakes of these nutrients (Asif. 2013b; Gaby. 1984; Gaby. 1994). Larger doses of Vit B6 could be considered for patients whose epilepsy is not effectively restricted by other treatments.

REFERENCES


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