REVIEW
Volume: 6 Number: 2 October 2016

The Role of Nutrients in Epilepsy

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Abstract

Conventional treatment for epilepsy is primarily based on anti-epileptic drugs (AEDs), and often, epilepsy patients must endure significant clinical experimentation to find a regimen that works for them. Most importantly, not all patients will respond well to AEDs, either due to a lack of effectiveness or due to side effects. Research has shed light on aspects of epilepsy that remain underappreciated by the conventional establishment.

For example, magnesium is a well- known anticonvulsive agent, and studies show that magnesium deficiency is associated with epilepsy; intravenous magnesium can effectively control different types of seizures as well.[1,2,3] However, the efficacy of supplemental magnesium has historically been limited in the context of conditions involving the central nervous system due to the inability of most types of magnesium to efficiently cross the blood-brain-barrier. Recently, though, scientists have developed a groundbreaking new form of supplemental magnesium, called magnesium-L-threonate, that elevates brain magnesium levels more than conventional types of magnesium.[4]

Introduction

People with epilepsy have a substantially higher mortality rate than the general population. This is attributable to a phenomenon known as sudden unexplained death in epilepsy patients (SUDEP). SUDEP is unexpected and non-traumatic and occurs in approximately 1% of epileptics.[5] It has no clear anatomical or toxicological cause, although it may be due to cardiac arrhythmias triggered by epileptic electrical activity. One of the most important things that epileptics can do to lower their risk of SUDEP is to improve the control of their disease, which for many patients can be achieved by changing their diet and taking supplements in addition to taking their anti-epileptic drugs. Sleeping on the back may also lower the risk of SUDEP.[6]

Neurobiology of seizures

The brain contains billions of neurons, which are in constant communication with one another. During nerve cell signaling or firing, neurotransmitters are released into the synapses to carry the signals. Neurotransmitters influence the action of neurons, either by exciting or inhibiting firing of neurons. The firing of neurons is mediated by electrical signals and as a result, abnormal electrical activity can cause uncontrolled neuron firing, leading to seizures.

Epileptic seizures are caused by a disruption in electrical activity among neurons in the cerebral cortex, the most highly developed part of the human brain. Although seizures emanate from the brain, there is a complex interaction between the autonomic nervous system and the central nervous system with regard to seizures.

Role of minerals and Reactive Oxygen Species in epilepsy

Electrolytes are minerals, such as sodium and potassium, which have an electrical discharge when dissolved in the body's fluids. The human brain relies on these minerals to generate the electrical currents needed for neurons to function and communicate. Consequently, alterations in the levels of these electrolytes can severely affect the electrical activity in the brain and trigger seizures in epileptics.

Hyponatremia was associated with increased frequency of seizures in a cross-sectional study of 363 patients in a county

hospital.[7]New onset epileptic seizures in a 54 years old woman who consumed a large amount of soft drink were described in a case report; her seizures were attributed to a sudden drop in sodium levels due to excessive fluid consumption.[8]

Magnesium and calcium deficiencies can also trigger or exacerbate seizures in epileptics.[9]

Reactive Oxygen Species (Free radicals) may play a role in epilepsy. [10] These compounds have the ability to damage proteins, DNA and the membrane of cells, potentially causing neurons to fire erratically leading to a seizure. Many factors can induce production of free radicals, including head trauma and neurodegenerative diseases as well as normal cellular metabolism.[11] Mitochondria, the cellular energy cores in which adenosine triphosphate (ATP) production takes place, are the primary source of free radicals within the body. With aging, the efficiency and integrity of these vital organelles begins to falter, leading to increasing oxidative stress and cellular degeneration. With regard to epilepsy, a relevant consequence of age-related mitochondrial dysfunction is cellular membrane damage, which can impair cellular communication, potentially leading to seizures. Indeed, experimental models indicate that animals genetically prone to a poor ability to quench mitochondrial free radicals are more likely to have seizures than normal animals.[12] Moreover, in humans, heritable defects in the mitochondrial genome cause a subclass of epilepsy called mitochondrial epilepsy.[13]

Role of Nutrients & elements in epilepsy

(A) Vitamins

Long term use of AEDs can affect vitamin and mineral status in the body of an epileptic. For instance, patients taking AEDs have significantly lower levels of Vitamin D in their blood.[14] This is because many AEDs increase the activity of a liver enzyme known as cytochrome P450, which also breaks down vitamin D. Vitamin D is essential for the absorption of calcium; consequently, patients taking AEDs absorb less calcium in their diet, which increases their risk of developing osteoporosis. Patients who are taking AEDs may need to take vitamin D and calcium supplements.[15]

Anti-epileptic drugs have also been shown to reduce levels of several B vitamins, including folate and vitamins B6 and B12.[16] These vitamins are critical for controlling metabolism in the body; low levels of these vitamins can also lead to low red blood cell levels, causing fatigue and pallor. One of the most serious consequences of the low folate levels caused by AEDs is high levels of the compound homocysteine, a risk factor for heart disease.[16,17,18] Elevated levels of homocysteine have been implicated in the increased risk of heart disease seen in epileptics. Moreover, some studies have indicated that elevated homocysteine may contribute to AED resistance or increase seizures in epileptics.[19] Based on these findings, some researchers call for routine supplementation with the B vitamins, especially the metabolically active form of Folic Acid, **L-methylfolate**, to reduce homocysteine levels.[20] Folate deficiencies can also lead to seizures, particularly in infants.

Impaired folate transport in the body can be a cause of seizures that do not respond well to typical treatments.[21]

Some forms of epilepsy are directly linked to vitamin B6 deficiencies; these convulsions known as pyridoxine-dependent seizures, can only be treated with high doses of vitamin B6.[22] Low vitamin B6 levels are also associated with general epilepsy. Even in patients without pyridoxine-dependent seizures, low levels of pyridoxine might increase seizure sensitivity, although more research needs to be done to determine if pyridoxine can treat seizures.[23] Some types of seizures cannot be

treated with pyridoxine, but they can effectively have managed with pyridoxal-5-phosphate, the biologically active form of vitamin B6.[24]

Vitamin K deficiency is increased in neonates of mothers receiving enzyme-inducing antiepileptic drugs and vitamin K1 treatment decreases the frequency of vitamin K deficiencies in these neonates.[25] It is widespread clinical practice to administer vitamin K to pregnant women and then to their newborns. This is certainly appropriate for women taking enzyme-inducing drugs; it is not known whether women taking other drugs require this regimen, but it seems prudent to follow it until more is known. Fourteen pregnant epileptic women received 20mg/day vitamin K1 for two weeks before delivery. No haemorrhages occurred in babies and prothrombin times were all normal at birth. This study suggested that vitamin K1 should be administered routinely to drug-treated epileptic women near the end of pregnancy.[26]

(B) Antioxidants

Antioxidants such as vitamin E, vitamin C and selenium are able to mitigate mitochondrial oxidative stress in the brain and other tissues, lowering seizure frequency in various types of epilepsy.[27] Animal models have shown that alpha-tocopherol alone is able to prevent several types of seizures.[28] Epileptics are also more likely to have low vitamin E levels, though this may be a result of taking anti-epileptic drugs.[29]

(C) Minerals

Calcium

Calcium is a very important mineral for the normal functioning of brain cells, and low levels of calcium can cause seizures. A deficiency of magnesium, a mineral that interacts with calcium, may cause low blood calcium and therefore seizures.

Magnesium

Magnesium deficiency can result in lowered immunity, improper muscle function, and impaired digestion. Nerves may become ultra sensitive to pain and production of new protein is impaired. Magnesium requires adequate amounts of vitamin B6 in order to be absorbed by the tissues. People with epilepsy have been shown to have significantly lower magnesium levels as compared to the general population, with seizure activity correlating with the level of hypomagnesemia. Magnesium has been shown, in uncontrolled trial studies, to be of benefit in the control of studies. A study showed that magnesium deficiency induces muscle tremors and convulsive seizures; success was reported in controlling the seizure activity of thirty patients with epilepsy using magnesium.[30]

30 children with epilepsy experiencing tonic-clonic or absence seizures were given 450mg of magnesium daily, and their anticonvulsant medications were discontinued. 29 reportedly showed significant improvements in seizure control. A thirteen year old child who had a ten year history of uncontrollable seizures had shown signs of retardation. After receiving magnesium, his seizures stopped and his mental capacity improved.[31]

Zinc

Zinc plays an important role in blood sugar balance, protein synthesis, brain function, and the immune system as well as other aspects of health. Children with epilepsy have been found to have significantly lower levels of serum zinc, especially those with West or Lennox-Gastault syndrome. More important, it appears that people with epilepsy may have elevated copper-to-zinc ratio. Seizures may be triggered when zinc levels fall. Although the exact role of zinc, or the copper-to-zinc ratio is not clearly understood, it appears that anticonvulsants may cause zinc deficiency, either by reducing zinc absorption in the intestines or by causing

diarrhea. Therefore, zinc supplementation may be warranted.[32]

(D) Essential Fatty Acids

Polyunsaturated Fatty Acids (PUFAs), such as omega-3-fatty acids, are a type of essential fat that play an important role in maintaining a healthy central nervous system. Animal studies have suggested that PUFAs, including omega-3 and some omega-6 fatty acids, may be able to modulate neuronal excitability.[33] This is further supported by the fact that children on the ketogenic diet often have higher levels of PUFAs in their cerebrospinal fluid, which suggests that increased PUFA levels is one of the ways that the ketogenic diet prevents seizures.[34] Clinical trials in adults have yielded mixed results. In one such study, 57 epileptic patients were given 1 g EPA and 0.7 g DHA daily. Seizure activity was reduced over the first six weeks, although the effect was temporary. The researchers called for more in depth studies, with larger doses and larger observational groups.[35]

(E) Resveratrol

Resveratrol, derived from red grapes and Japanese knotweed, and the plant Bacopa monnieri both appear to be promising in the management of seizure-related neurotoxicity. Resveratrol and bacopa-derived compounds have extensively studied in experimental settings and consistently shown to guard against neuronal damage. [36] In the context of epilepsy, numerous mechanisms by which resveratrol might prevent seizures have been proposed, and indeed, in an animal model resveratrol prevented chemical induced seizures; studies on epileptic humans though have not been performed.[37, 38] Likewise, bacopa has been the subject of several animal model experiments, many of which have received a clear benefit relating to seizure frequency and post –seizure brain damage. [39]

Role of Ketogenic diet in the treatment of Epilepsy in children

The ketogenic diet, initially described by Hugh Conklin, a Michigam pediatrician, is a high fat, low carbohydrate, and normal protein diet that has been used for the treatment of medically refractory childhood epilepsy since the 1920s'.[40] Although its use became less frequent with the introduction of anticonvulsant medications, the diet has regained recognition over the past 15 to 20 years. Medical associations have not been enthusiastic to develop guidelines and to endorse the diet. As a result, clinical centres follow different protocols, making comparisons and evaluation of the diet's efficacy difficult.

The ketogenic diet includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive but more effective.[41] The ketogenic diet predisposes to nutritional deficits in energy, proteins, minerals, and vitamins and excess in lipids, saturated fat, and cholesterol. Use of such an unbalanced diet requires particular attention to implementation and monitoring. Strict adherence to the dietary plan is required, and even small amounts of food beyond the diet or deviation in food preparation might cause considerable reduction in the efficacy of the diet.

Meal plans are patient tailored and can include heavy cream, bacon, eggs, tuna, shrimp, vegetables, mayonnaise, sausages, and other high fat and low carbohydrate products. Patients are not allowed starchy fruits or vegetables, bread, pasta, grains or sources of simple sugars. The food preparation may be onerous for parents and patients, who may pay great attention to selecting, weighing and cooking every meal or dietary component. While on the diet, patients should also receive recommended daily intakes of vitamins and minerals (in sugar-free formulations), as well as calcium supplementation. Precise quantities of food for the diet and meal plans are derived using individual patient data (age,weight etc) in

computer applications such as the ketoCalculator.[42]

At least 1 g of protein per kg of body weight should be supplied daily to children older than 3 years of age (and more to younger children) to preserve growth.

Children on the diet need to be seen monthly by registered dietitians, with adjustments to diet according to each child's need s to allow for normal growth and weight gain.

Mechanism of action:

Despite nearly a century of use, the mechanisms underlying the clinical efficacy of the ketogenic diet remains unknown. Several mechanistic theories have been proposed:

1) Modification of the tricarboxylic acid cycle to increase gamma-aminobutyric acid synthesis in the brain,
2) limit reactive oxygen species generation,
3) and boost energy production in brain tissue. [43]

As a result, hyperpolarization of the neurons occurs, stabilizing synaptic function and increasing resistance to seizures.

Based on the tricarboxylic acid mechanism, the ketogenic diet is an appropriate first-line therapy for patients with seizures associated metabolic disorders such as glucose transporter protein deficiency (ie De Vivo disease) and pyruvate dehydrogenase complex deficiency.[44] Another indication for ketogenic diet is intractable childhood epilepsy.

Clinical trials:

A recently published RCT showed the efficacy of the ketogenic diet in children.[45] Neal et al demonstrated in an RCT of 145 children, aged 2 to 16 years old who had at least daily seizures and had failed to respond to at least 2 antiepileptic drugs for 3 months , that the mean percentage of baseline seizures was significantly lower in the diet group than in the control group. [45] Twenty-eight children (38%) in the diet group had greater than 50% seizure reductions compared with with 4(6%) controls, and 5 children (7%) in the diet group had greater than 90% seizure reductions compared with no controls. In another RCT, Neal et al, in 149 children with intractable epilepsy, that both classical and medium-chain triglyceride ketogenic diet protocols are comparable in efficacy and tolerability and that both ways of implementing the diet have their place in the treatment for childhood epilepsy.[46]

As for adults, a prospective study of 9 adult patients with a mean of 28 yrs demonstrated extremely low adherence; only 2 subjects concluded the study owing to an early mean dropout at 8 weeks.[47]

Benefits and side effects

Patients on a ketogenic diet become more alert and exhibit considerable improvements in attention, comprehension, activity levels, and endurance. [48]

Most of the side effects from the ketogenic diet are related to energy and nutrient deficiencies. Lack of protein, carbohydrates, and other nutrients can result in lack of weight gain and growth inhibition, especially at a young age. Inadequate calcium can further impair bone mineralization in children already at risk of osteopenia due to antiseizure therapy. Lack of fibre in the diet causes constipation. Acidosis is also commonly observed. Less common are kidney stones and hyperlipidaemia.[49] Adjustments to the diet (eg increased protein and polyunsaturated fat) can be made in child with high lipid concentrations. Serious adverse effects include coma and obtundation.[44] Rare side effects include cardiomyopathy, prolonged QT syndrome, vitamin and mineral deficiencies, pancreatitis, basal ganglia injury, and brusing.[50]

Regular admissions and easy access to appropriate health care providers are needed for follow-ups and monitoring side effects.

Administration of the ketogenic diet

Initiation of the ketogenic diet is preceded by a 24 to 48 hours fast, with the patient being hospitalized. During the fast, the patient can drink unsweetened beverages and water, and can eat unsweetened gelatin. Alternatively, Bergqvist et al have shown that slow initiation of the ketogenic diet can result in fewer side effects and is overall better tolerated, maintaining the same efficacy.[51]

Contraindications such as Ɓ-oxidation defects, liver disease, or metabolic disease interfering with glucose or ketone homeostasis must be excluded before initiation of the diet.

The diet is introduced by starting with one-third of calories per meal, increasing to two-thirds of calories per meal and to the total amount of calories per meal every 24 hours.

Patients are discharged when the total amount of calories per meal is reached and well tolerated, typically 2 to 3 days after initiation of the diet.

If the diet is initiated without hospitalization, adequate facilities must be available to instruct families on meal preparation and monitoring techniques.

Summary

Most epileptics take anti-epileptic drugs(AEDs). These drugs can affect vitamin status and raise homocysteine levels. Patients taking AEDs are advised to supplement with calcium and vitamin D to help prevent AED-induced osteoporosis and to regularly monitor their homocysteine levels. If homocysteine levels are elevated, patients should take steps to reduce homocysteine by using B vitamins, including L-methylfolate, vitamin B12, and vitamin B6.

Patients on a ketogenic diet are advised to take a high potency multivitamin to ensure adequate availability of nutrients. In addition, a high intake of fibre (more than 20 g daily) is recommended to reduce fluctuations in blood sugar levels.

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