REVIEW

Volume: 6 Number: 2 October 2016

Essential Role of Vitamins in Epilepsy

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Abstract

In their life it has no respect for age, sex, race or social class. Seizures tend to develop in childhood or by late adolescence, but it can again arise after the age of 65[1]. Epilepsy is common neurological condition in the world and can affect anyone at any time.

INTRODUCTION

In many work it was found that five percentages of people have a single seizure sometime in their life and as per a recent study, 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions. The study also estimated a median prevalence of 1.54% for rural and 1.03% for urban in developing countries [2].In Indian Scenario higher rates of epilepsy reported for the male gender, rural population, and low socioeconomic status and despite its varied aetiology (unknown and known), majority of the epilepsy are manageable in nature [3].

THIAMINE(B1)

Thiamine, also known as vitamin B1, is a colourless compound with the chemical formula C12H17N4OS. This vitamin only synthesizes by bacteria, fungus or plants. It is soluble in water and insoluble in alcohol, it also decomposed if heated. Thiamine was first discovered by Umetaro Suzuki in Japan when researching how rice bran cured patients of Beriberi. It plays a key role in intracellular glucose metabolism and it is thought that thiamine inhibits the effect of glucose and insulin on arterial smooth muscle cell proliferation. Thiamine plays an important role in helping the body convert

nervous and digestive systems [4].Thiamine cannot be stored in the body; however, once absorbed, the vitamin is concentrated in muscle tissue [4]

The main source of thiamine is in dried brewers yeast and there are other good sources including (a) Meats: pork, lamb, poultry, eggs, nuts.(b) In vegetables legumes, whole grain cereals (the thiamine is present in the germ of the grain) are the most important dietary sources of thiamine, whole grains contain more thiamine than refined grains, as it found mostly in the outer layers of the grain and in the germ, for example 100 g of whole-wheat flour contains 0.55 mg of thiamine, while 100 g of white flour contains only 0.06 mg of thiamine [5].

Deficiency in human can causes various neurological and systemic diseases like Korsak off is syndrome, optic neuropathy and a disease called beriberi that affects the peripheral nervous system (polyneuritis) and/or the cardiovascular system. Thiamine deficiency has a potentially fatal outcome if it remains untreated [6].Apart of various neurological disorders, thiamine deficiency plays important role in development of epilepsy. In a study where sixteen of 50 consecutive neurological patients with a diagnosis of thiamine deficiency showed epileptic 10 or epileptiform 6 manifestations. It appears that thiamine deficiency may provoke epileptic phenomena in those patients who have subclinical predisposition for seizures. The presence of irrigative activity on electroencephalographic recordings in the

patients may be a consequence of a vitamin B1 deficiency state[7]. In addition, thiamine deficiency has been reported in patients with epilepsy and its supplementation may be necessary to prevent or reverse the effects of its deficiency. In a study it was found that 31% of the patients chronically treated with phenytoin had subnormal blood thiamine levels up to 30% at baseline assessment. Further the result after thiamine therapy improves neuropsychological functions, such as visuo-spatial analysis, visuo-motor speed and verbal abstracting ability in these patients [8].

PYRIDOXINE (B6)

Pyridoxine is water-soluble vitamin, its sources include meat, nuts, and whole-grain products (especially wheat). The deficiency usually occurs in conjunction with inadequate intake of other B vitamins due to poor diet or malabsorption states, Isolated pyridoxine dependency can occur, during treatment with isoniazid, which is a pyridoxine antagonist. The other conditions of deficiency are when pyridoxine requirements are increased in the presence of other drugs, including penicillamine, contraceptive steroids, and hydralazine [9]. Clinical features of deficiency in young infants include abnormal CNS activity like irritability, aggravated startle response, seizures and in gastrointestinal distress like distension, vomiting, diarrhoea. Their manifestations include anaemia, peripheral neuropathy, and dermatitis [10,11]. Consider pyridoxine dependency in the differential diagnosis of neonatal seizures when other more common causes have been eliminated. Treatment consists of pyridoxine 5 mg intramuscularly followed by 0.5 mg per day orally for 2 weeks to correct dietary deficiency and for rapid treatment pyridoxine, 100 mg intramuscularly, is recommended [12]. Pyridoxine-dependent seizure (PDS) is a rare autosomal recessive disorder that usually presents with intractable seizures in early stages of life. The history suggestive severe convulsive disorders in family also and their diagnosis can have made on basis of symptoms, if seizures of unknown origin in a previously normal infant without an abnormal gestational or perinatal history. The occurrence of long-lasting focal or unilateral seizures along with irritability, restlessness, crying and vomiting preceding the actual seizure with partial preservation of consciousness.

The seizures can be completely controlled by administration of large doses of vitamin B6, but if the condition is not treated promptly, irreversible neurological damage may occur. For confirmations of PDS, when parenteral pyridoxine injection administer, seizures stop within a few minutes and epileptic EEG discharges subside within a few hours after the intravenous injection of 50–200 mg of pyridoxine [13,14]. Pyridoxine should be administered under EEG monitoring as a diagnostic test in all cases of convulsive disorders in infants and young children in which no other diagnosis is evident. Intravenous administration of vitamin B6 to infants after a long period of convulsions has been followed in some cases by acute hypotonia and apnoea; therefore, resuscitation equipment should be available during a trial of intravenous vitamin B6 [15,16]. Alternatively, the disorder may be diagnosed by giving 15 mg/kg per day of oral pyridoxine to a patient who experiences frequent seizures and noting complete control of the seizures within a week or so[17]. Once the diagnosis is confirmed, maintenance therapy (25–200 mg/day) should be continued indefinitely and doses increased with advancing age or when intercurrent illnesses occur. It is also recommended that women who have had a child with vitamin B6 dependency receive vitamin B6 supplements during subsequent pregnancies [18,19].

A related entity has also been described in a few patients in those seizures responsive to pyridoxal phosphate but resistant to pyridoxine [20]. In another study [21]it was found that pyridoxal

phosphate is better than pyridoxine in the treatment of intractable childhood epilepsy, particularly in the treatment of infantile spasms.

Finally, in patients with epilepsy and without pyridoxine dependency, vitamin B6 deficiency has been observed, however at the moment, there is not enough evidence to suggest that vitamin B6 supplementation might help the treatment of patients with non vitamin B6-dependent refractory seizures [22]. In addition, supplementation with 80–200 mg/day pyridoxine can reduce serum phenytoin and phenobarbital levels [23,24], and long-term administration of 500 mg/day or more of pyridoxine may produce neurotoxicity in adults, which could presumably occur at lower doses in children [25].

FOLIC ACID (B9)

Seizures may occur in some infants with cerebral folate deficiency. In this disorder, the seizures begin between 2 h and 5 days after birth, although intrauterine hiccup can be the first symptom. Myoclonic and clonic seizures, sometimes associated with apnea, have been described. Affected neonate may be irritable, jittery, obtunded, or even becomes comatose. In the neonatal period it manifests a discontinuous background pattern and multifocal spikes or sharp waves. This syndrome is probably caused by impaired transport of folate across the blood–brain barrier into the central nervous system. The transport defect can be overcome by administration of folinic acid (an active form of folic acid), which bypasses the blocked folate transport mechanism. The disorder of folinic acid-responsive seizures is lethal when no specific treatment is initiated. Folinic acid administration should be considered in all cases of refractory neo- natal seizures in which no other diagnosis is evident. The starting dose of folinic acid is usually 2.5 mg twice per day, and can be gradually increased up to 8 mg/kg/day. Seizures commonly cease within 24 h after folinic acid is initiated. Withdrawal of the treatment leads to seizure recurrence within a few days. Oral folinic acid should be continued indefinitely (2.5–5 mg/kg/day). Most children require continuation of antiepileptic medication as well. The prognosis is poor even with folinic acid therapy and seizure control [26,27].

In patients with seizures not due to cerebral folate deficiency, folic acid (or its derivatives) supplementation is of little or no benefit with respect to seizure control. However, folate deficiency is common in patients with epilepsy and may have negative effects on other aspects of health and therefore, its correction is desirable.

SUPPLEMENTATION OF VITAMINS

It was observed that low dose of folate supplementation may prevent carbamazepine-induced leukopenia or anaemia in patients with epilepsy. In one randomized clinical trial of carbamazepine-treated children[28], white blood cell and polymorpho nuclear cell counts were significantly higher in patients who received folate supplementation respectively and the incidence of neutropenia was cut almost in half (17.1% vs. 9.8%). Haemoglobin concentration dropped in carbamazepine-only treated children, but rose slightly in children who received folate supplementation as well; these changes were also significant. These findings could be helpful if considered in the management process of the patients who are prescribed carbamazepine, especially in patients who are at more risk for carbamazepine-induced leukopenia (e.g., those with borderline low white blood cells, neutrophil, or monocyte counts at baseline) [29]. While correction of folate deficiency is desirable, administration of large doses of folic acid can decrease blood levels of phenytoin, phenobarbital, and carbamazepine, potentially interfering with seizure control [30,31]. The impact of adding folic acid to a stable phenytoin regimen in an effort to correct folate deficiency

is often under- estimated. The mean decrease in total serum phenytoin level after the addition of 1 mg oral folic acid is about 20% and after adding 5 mg of oral folic acid might be as high as 40%. Pharmacokinetic studies of this interaction strongly suggest that folic acid is a cofactor in the metabolism of phenytoin. Higher levels of folate increase the affinity of metabolizing enzymes, thus greatly increasing the efficiency of phenytoin degradation[30].

Though evidence is lacking, the use of high dose folic acid supplements in women with epilepsy before conception and during pregnancy is generally recommended to potentially prevent some of the teratogenic effects of AEDs particularly neural tube defects.

BIOTIN (B7)

Biotin deficiency has been reported in patients with epilepsy. This has been attributed to antiepileptic therapy (e.g., with carbamazepine, phenobarbital, and phenytoin [31].

Biotin supplementation might reduce seizure frequency in patients with inborn errors of biotin metabolism. Biotinidase deficiency is an autosomal recessive genetic disorder in which absence of biotinidase leads to infantile or early childhood encephalopathy, seizure disorder, dermatitis, alopecia, neural deafness, and optic atrophy. Treatment with biotin results in clinical recovery and normalization of the biochemical, neuroradiological, and neurophysiological parameters [32].

CARNITINE

Treatment of patients with valproic acid, particularly in combination with other antiepileptic drugs (AEDS) reduces total and free carnitine concentrations and increases plasma ammonia concentrations. In one prospective study [33], two out of 13 valproate-treated children developed clinical symptoms (e.g., fatigue) and biochemical evidence of carnitine deficiency. In four others, an asymptomatic bio- chemical deficiency was found. If a patient complains of fatigue during prolonged valproic acid treatment, some practitioners advise carnitine supplementation. In addition, there are some preliminary data that support the hypothesis that l-carnitine treatment significantly enhances the survival of patients with severe valproate- induced hepatotoxicity[34]. Oral l-carnitine supplementation is also suggested (level C evidence) for infants and young children receiving valproate, especially those younger than 2 years with a complex neurological disorder who are receiving multiple AEDs, patients who have multiple risk factors for hepatotoxicity (e.g., neurological impairments, poor nutrition, failure to thrive, chronic illness, receiving multiple AEDs), and those receiving dialysis [35].

VITAMIN D

Biologically active analogues, resulting in decreased bone mineralization, decreased intestinal calcium absorption, increased calcium mobilization from the skeleton to maintain eucalcemia, and decreased bone density [36]. Valproate can also decrease bone mineral density with an unclear mechanism [37]. Patients with epilepsy who take enzyme inducing drugs or valproate should maintain a balanced diet rich in calcium and vitamin D; many practitioners recommend supplementation with calcium and vitamin D daily. Evidence suggests that vitamin D might have some antiepileptic effects. In one animal study [38], it was observed that administration of 1,25- dihydroxyvitamin D3 resulted in the elevation of hippocampal seizure threshold levels in rats. In addition, in one small placebo controlled clinical trial[39], it was observed that the frequency of epileptic seizures significantly decreased in nine patients taking vitamin D as add-on-drug compared with 14 patients taking placebo in addition to their AEDs. The effect was unrelated to changes in serum calcium or magnesium levels.

VITAMIN E

Vitamin E deficiency has been reported in patients with epilepsy, though its clinical significance remains uncertain. This deficiency has been attributed to antiepileptic therapy[40]. Evidence with regard to antiepileptic effects of vitamin E is contradictory. In one animal study[41],the anticonvulsant effects of d-alpha-tocopherol (vitamin E) were studied in four animal seizure models. It delayed the onset of seizures in the intracerebral ferrous chloride model, but not in the animal models commonly used to screen for anticonvulsant drug actions. However, a double-blind placebo-controlled, cross-over trial[42], with vitamin E as add-on therapy in 43 patients with uncontrolled epilepsy demonstrated no efficacy with regard to seizure control.

Vitamin K

The incidence of vitamin K deficiency is increased in neonates of mothers receiving enzyme-inducing AEDs and antenatal vitamin K1 treatment decreases the frequency of vitamin K deficiency in these neonates[43]. It is widespread clinical practice to administer vitamin K to pregnant women and then to their new-borns. 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.

OTHER NUTRIENTS

Manganese deficiency has been reported in patients with epilepsy, though it does not appear to correlate with seizure frequency or the type, dose, or plasma levels of AEDs [44].Omega-3 fatty acids increase seizure thresholds, and lower inflammatory mediators, which are increased in patients with epilepsy. Linolenic acid prevents kainate-induced seizures and neuronal death and has neuro- protective effects [45]. In a double-blind study that included 57 adults [46], supplementation with fish oil, providing omega-3 fatty acids, reduced seizure frequency during the first 6 weeks of treatment, but the beneficial effect was not sustained thereafter.

In summary, the following vitamin may help modulate neuronal excitability: vitamin B-complex vitaminThiamine (B1)75-125 mg/day, Riboflavin (B2)50 mg/day, Niacin (B3)50-190 mg, Folate400-1000 mcg/day,Vitamin B6 (preferably as pyridoxal-5-phosphate)75-105 mg/day,Vitamin B12300-600 mcg, Biotin300-3000 mcg, Pantothenic Acid100-600 mg/day, Vitamin D5000-8000 IU daily, Natural Vitamin E100-400 IU alpha-tocopherol, 200 mg gamma-tocopherol, Vitamin C1000-2000 mg daily. Though there are some controversial reports, those are not always favour of recommending these vitamins in all epileptic patients. In contrary some reports found that these might harm in long term prescriptions.

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