

Role of various vitamins in the patients with epilepsy

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Abstract

In this review, we study the effect of various vitamins in the epileptic patients. These vitamins are generally may reduce seizure frequency and treating adverse effect of anticonvulsant drugs. Supplementation with folic acid, vitamin B6, vitamin E, biotin, vitamin D, may be needed to prevent or treat deficiencies resulting from the use of anticonvulsant drugs. Thiamine may improve cognitive function in the epileptic patients. Vitamin K1 has been recommended near the end of pregnancy for women taking anticonvulsant drugs. Vitamins therapy is not a substitute for anticonvulsant medications.

Key words: Vitamins, Epilepsy, Nutrients, Diet.

1. Introduction:

It is important that people with epilepsy follow a nutritious and well balanced diet. Good nutritional habits and healthy lifestyle is an important to optimal seizure control. However, no special diet is prescribed for epilepsy patients. But to avoid dietary deficiencies, ensure proper intake of nutrients, containing adequate vitamins (folic acid, Vitamin B1, Vitamin D Vitamin B6, Vitamin B12 Vitamin E and vitamin K), inorganic salts (calcium, magnesium and manganese) and other micronutrients¹⁻³. If patient have some other condition (like diabetes) in addition to epilepsy that requires a special diet. Problems can generally be avoided with a proper diet⁴⁻⁸. However, in rare cases, more serious problems may arise due to deficiency of vitamins. For example, anemia can result from severe folic acid deficiency. Weak bones are related to inadequate amounts of vitamin D. Vitamin supplements can be prescribed as necessary. Self-prescribed “mega-vitamin” therapy will do no good and could be harmful. For example, excessive folic acid intake may actually decrease seizure control.

2. Role of vitamins in epilepsy

2.1 Thiamine (B1): Severe thiamine deficiency can cause seizures in both alcoholic and non-alcoholic patients; these seizures are reversible with thiamine supplementation. Low thiamine status was found in epileptic patients^{9,10} and consecutive neurological patients. In a placebo-controlled trial, supplementation of epileptic patients with 50 mg thiamine daily for six months was associated with significant improvements¹¹. The research suggested that thiamine deficiency might be considered as one possible cause of late-onset epilepsy. 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. The patients chronically treated with phenytoin had subnormal blood thiamine levels and had low folate.

2.2 Pyridoxine (B6): Pyridoxine-dependent seizure (PDS) is a rare autosomal recessive disorder that usually presents with intractable seizures in early stages of life. The seizures can be completely controlled by administration of large doses of vitamin B6. Clinical seizures stop within a few minutes and epileptic electroencephalographic (EEG) discharges subside within a few hours after the intravenous injection of 50–200 mg of pyridoxine^{12,13}. 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 apnea^{14,15}. Alternatively, the disorder may be diagnosed by giving 15 mg/kg/day of oral pyridoxine to a patient who experiences frequent seizures and noting complete control of the seizures within a week or so¹⁶. 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 vitaminB6 dependency receive vitamin B6 supplements during subsequent pregnancies¹⁷⁻¹⁹. In addition, it was observed that pyridoxal phosphate is better than pyridoxine in the treatment of intractable childhood epilepsy, particularly in the treatment of infantile spasms²⁰. 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 seizures²¹. In addition, supplementation with 80–200 mg/day pyridoxine can reduce serum phenytoin and

phenobarbital levels^{22,23} 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 children²⁴. In the early 1950s, numerous infants in the United States developed convulsions traced to the use of a formula that was deficient in pyridoxine^{25,26}. Seizures also occurred in an infant fed exclusively on powdered goat's milk, which had undetectable levels of the vitamin. The seizures resolved after supplementation with vitamin B6²⁷. Vitamin B6 deficiency has been found in a high proportion of patients with epilepsy. In a study, patients with severe epilepsy, had a reduced serum concentration of pyridoxal²⁸. Low levels of vitamin B6 may be due in part to treatment with phenytoin, which has been associated with evidence of reduced vitamin B6 status (i.e., increased xanthurenic acid excretion following a tryptophan load)²⁹. However, other factors may be involved as well, since there does not appear to be a strong relationship between low vitamin B6 levels and use of any specific anticonvulsant medication. Vitamin B6 supplementation is clearly beneficial in cases of vitamin B6-dependent seizures. Some studies have demonstrated improvements in patients with non-vitamin B6-dependent epilepsy as well, although the research has produced conflicting results.

2.3 Vitamin B6-dependent Seizures: Vitamin B6-dependent epilepsy is a rare inherited disorder that usually presents with intractable seizures in the first six months of life. The seizures can be completely controlled by the large doses of vitamin B6^{30,31} but if the condition is not treated promptly irreversible neurological damage may occur. The diagnosis of vitamin B6 dependency can be established by intravenous administration of pyridoxine, which results in cessation of seizures within minutes. Most patients can subsequently be maintained on 25-50 mg/day oral pyridoxine, although one child required 200 mg/day³². Long-term supplementation is necessary; discontinuation of pyridoxine after several years of good seizure control has resulted in death from status epilepticus. Some patients with vitamin B6-dependent seizures present with an atypical picture, including later onset (up to 19 months of age)³³, a seizure-free period before administration of pyridoxine, a long remission after withdrawal of pyridoxine, and an atypical seizure type. It is also recommended that women who have a child with vitamin B6 dependency receive vitamin B6 supplements during subsequent pregnancies.

2.4 Vitamin B6 for Non-vitamin B6-dependent Epilepsy: Vitamin B6 supplementation has been reported to be beneficial in some, but not all, patients with non-vitamin B6-dependent epilepsy. The children with epilepsy received 160 mg/day pyridoxine, the patients with laboratory evidence of vitamin B6 deficiency (i.e., increased urinary excretion of xanthurenic acid following a tryptophan load), had complete or partial amelioration of seizures, and some of these patients were able to discontinue anticonvulsant medication. Of the patients with a normal tryptophan load test, none responded to pyridoxine^{34,35}. Of children (ages 3-8 years) with epilepsy associated with impaired intellectual development, progressive emotional disturbances, and abnormal EEGs, all excreted elevated amounts of xanthurenic acid after a tryptophan load.

After administration of 60-160 mg pyridoxine daily, tryptophan metabolism became normal and substantial clinical improvement occurred³⁶. Pyridoxine (20 mg, 3-6 times daily) was given for an unspecified length of time to epileptic patients, ages 2-17 years. All patients had petit mal and one also had grand mal epilepsy. Seizures ceased five patients and became less frequent³⁷. Epileptic children received 160-200 mg pyridoxine daily for at least six weeks. Significant clinical improvement was seen in five cases²². A 23-year-old man with recurrent seizures presented with status epilepticus, which resolved immediately following intravenous administration of 60 mg pyridoxal phosphate. Prior to treatment, patient serum pyridoxine concentration was markedly decreased (80% below the lower limit of normal). Pyridoxine was given intravenously to infants and children with acute, recurrent seizures due primarily to acute infections. A dose of 30 or 50 mg/kg/day was administered over 2-4 hours and given for a few days. The treatment was rated "very effective" in patients receiving pyridoxine. Aside from transient flushing, no adverse effects were seen. In other studies, pyridoxine in doses of 20-100 mg/day orally^{39,40} or 300 mg/day parenterally³⁸ to produced no clinical improvement in patients with various types of epilepsy.

2.5 Pyridoxine versus Pyridoxal Phosphate: While most patients with vitamin B6-dependent seizures can be effectively treated with pyridoxine, some patients have only responded to pyridoxal phosphate, the biologically active form of vitamin B6¹⁹. The average effective oral dose of pyridoxal phosphate-responsive seizures was 30 mg/kg/day (range, 7-38 mg/kg/day), which was significantly higher than the average effective pyridoxine dose (18 mg/kg/day) in pyridoxine responders²⁰. Because of superior efficacy in certain cases, pyridoxal phosphate should be considered for first-line treatment of patients in whom a clinical trial of vitamin B6 is indicated. Pyridoxal phosphate should also be considered for patients with suspected vitamin B6-responsive seizures that are unresponsive to pyridoxine.

3. Vitamin B6 in Clinical Practice

Vitamin B6 should be tried in all infants and young children with intractable epilepsy. For children and adults whose seizures are well controlled on medication, moderate doses of vitamin B6 (such as 10-50 mg/day) may be considered to prevent possible drug induced vitamin B6 deficiency. Although larger doses might be appropriate in selected cases, high-dose vitamin B6 appears to interfere with some anticonvulsant medications. In one study, supplementation with 80-200 mg/day pyridoxine reduced serum phenytoin and phenobarbitone levels in epileptic children²². In addition, long-term administration of 500 mg/day or more of pyridoxine has resulted in neurotoxicity in some adults²⁴, which could presumably occur at lower doses in children. The supplementation with 600 mg/day vitamin B6 reversed phenytoin-

induced gingival hyperplasia in several patients; however, such high doses are probably excessive for most patients with epilepsy. Lower doses might be effective for phenytoin-induced gingival hyperplasia, particularly when used in combination with a folic acid mouth rinse. Patients being treated with vitamin B6 should probably also receive a magnesium supplement, in view of evidence that these nutrients work together and subjective reports that vitamin B6 supplementation increases the requirement for magnesium.

3.1 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)²¹. Biotin supplementation might reduce seizure frequency in patients with inborn errors of biotin metabolism. Biotinidase deficiency is an autosomal recessive genetic disorder. 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^{47,21}. Serum biotin levels were below normal in epileptic patients on long-term anticonvulsant therapy⁴⁸. Low biotin levels appear to result from an acceleration of biotin catabolism by phenytoin, carbamazepine, and phenobarbital^{49,50}. In addition, carbamazepine and primidone may inhibit intestinal absorption of biotin⁵¹. Interestingly, dermatitis and ataxia, side effects of many anticonvulsants, are also observed in patients with an inborn error of biotin-dependent enzymes. There is no evidence that biotin supplementation interferes with the effect of anticonvulsants. To the contrary, correction of biotin deficiency might reduce seizure frequency, as suggested by the fact that biotin responsive seizures have occurred in some patients with inborn errors of biotin metabolism⁵².

3.2 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. Electroencephalographic (EEG) recordings in the neonatal period manifest 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 neonatal 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 control⁴²⁻⁴³.

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. It has been observed that low dose of folate supplementation may prevent carbamazepine-induced leukopenia or anemia in patients with epilepsy. In one randomized clinical trial of carbamazepine-treated children⁴⁴, white blood cell and polymorphonuclear cell counts were significantly higher in patients who received folate supplementation and the incidence of neutropenia was cut almost in half. Hemoglobin 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)⁴⁵. 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^{46,21}. The impact of adding folic acid to a stable phenytoin regimen in an effort to correct folate deficiency is often underestimated. 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 appear to increase the affinity of metabolizing enzymes, thus greatly increasing the efficiency of phenytoin degradation⁴⁶. 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.

Seizures occur in some infants with cerebral folate deficiency, a syndrome that also includes slow head growth, psychomotor retardation, cerebellar ataxia, and other neurological abnormalities. This syndrome is 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. There are several case reports in which administration of folinic acid (2.5-20 mg twice daily in one study, 0.5-1.0 mg/kg body weight per day in another) resulted in improvement or complete control of seizures in infants^{41,53}. In patients with seizures not due to cerebral folate deficiency, folic acid supplementation is of little or no benefit with respect to seizure control, and may even exacerbate seizures in some instances. However, folate deficiency is common in patients with epilepsy and may

have negative effects on other aspects of health. Subnormal serum or erythrocyte folate concentrations have been observed in patients with epilepsy in different studies⁵⁴⁻⁵⁸. Low folate levels were found more frequently among inpatients than outpatients, and in those with coexisting psychiatric illness than those without psychiatric illness. Folate deficiency is due primarily to the use of anticonvulsant medications (e.g., phenytoin, valproate, carbamazepine, phenobarbital, and primidone), which interfere with folic acid absorption⁵⁹⁻⁶¹. While correction of folate deficiency is desirable, administration of large doses of folic acid can decrease blood levels of phenytoin, phenobarbital, and carbamazepine⁶²⁻⁶⁵, potentially interfering with seizure control. An increase in seizure frequency has been seen in some⁶⁶, but not all⁶⁷⁻⁶⁹, studies in which high-dose folic acid (5 mg three times per day) was given to drug-treated epileptic patients. In addition to interfering with anticonvulsant medication, high-dose folic acid itself may be epileptogenic. Intravenous administration of 14.4 mg folic acid induced a tonic-clonic seizure in one epileptic patient, although other patients experienced no adverse effects from 75 mg folic acid given intravenously⁷⁰. One woman with epilepsy had an increase in seizure frequency and severity after receiving 0.8 mg folic acid per day, which was prescribed because she was planning to become pregnant⁷¹. A cause-effect relationship in this case is uncertain. Based on these observations, modest doses of folic acid should be used to treat folate deficiency in epileptic patients. The pregnant epileptic women taking anticonvulsant drugs found that a folic acid dose of 100-1,000 mcg/day was sufficient to prevent folate deficiency and did not impair seizure control⁷². Folic acid has also been used to treat phenytoin-induced gingival hyperplasia. The use of a 0.1-percent folic acid mouth rinse for six months significantly reduced the severity of this condition, whereas a placebo was ineffective. Patients used 5 mL of the mouth rinse twice daily, spitting it out after rinsing for two minutes (should not be swallowed, 10 mg/day of folic acid). Oral, rather than topical, administration of folic acid (3-4 mg/day) produced little or no improvement in phenytoin-induced gingival hyperplasia^{73,74}.

3.3 Vitamin D: Some antiepileptic drugs may have negative effects on bone mineral density through a variety of mechanisms including inducing the hepatic cytochrome P450 system (CYP450) which promotes the metabolism of 25-hydroxyvitamin D (25-OHD) to less 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^{75,76}. Valproate can also decrease bone mineral density with an unclear mechanism. 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.

It was observed that administration of 1,25-dihydroxyvitamin D₃ resulted in the elevation of hippocampal seizure threshold levels in rats⁷⁷. In addition, it was observed that the frequency of epileptic seizures significantly decreased in patients taking vitamin D as add-on-drug compared with patients taking placebo in addition to their antiepileptic drugs⁷⁸.

Patients taking anticonvulsants are at increased risk of developing vitamin D deficiency, apparently because these drugs induce liver enzymes that inactivate vitamin D^{48,79}. Rickets, osteomalacia, and low bone mineral content^{78,80} have been reported in drug treated epileptic patients. In patients with osteomalacia resulting from the use of phenytoin and phenobarbital, the amount of vitamin D₃ needed to achieve positive calcium balance was approximately 975 IU/day⁸¹. In patients with low 25-hydroxyvitamin D levels who were taking phenytoin, carbamazepine, and phenobarbitone, either alone or in combination, the amount of vitamin D₃ required to maintain a normal serum 25-hydroxyvitamin D concentration (15 ng/mL or greater) ranged from 400 to 4,000 IU/day, with 72 percent of patients requiring 2,400 IU/day or more⁸².

3.4 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 therapy⁸³. The antiepileptic effect of vitamin E is contradictory. In one animal study⁸⁴, the anticonvulsant effects of alpha-tocopherol (vitamin E) in animal seizure models. However, a placebo-controlled, cross-over trial⁸⁵ with vitamin E as add-on therapy in patients with uncontrolled epilepsy demonstrated no efficacy with regard to seizure control. Erythrocyte or plasma vitamin E concentrations were lower in children with epilepsy than in healthy controls. Vitamin E levels were lower in children receiving multi-drug therapy than in children receiving single-drug therapy^{86,87}. In some studies, vitamin E supplementation reduced seizure frequency.

Twenty-four children (ages 6-17 years) with treatment-resistant epilepsy were randomly assigned to receive, in double-blind fashion, 400 IU/day alpha-tocopheryl acetate or placebo for three months. Of the 12 patients given vitamin E, 10 had a greater-than-60-percent reduction in seizure frequency (of that 10, six had a 90-100% reduction). None of the patients in the placebo group had a greater-than-60-percent reduction in seizure frequency ($p < 0.05$ for the difference in response rate between groups). Vitamin E treatment had no effect on plasma levels of anticonvulsant medications. Thirty-five epileptic children and adults were randomly assigned to receive, in double-blind fashion, 250 IU/day vitamin E or placebo for three months. Anticonvulsants were continued as previously. Of the 12 adults receiving vitamin E, eight had a decrease in seizure frequency, two had an increase, and two were unchanged. Of the children receiving vitamin E, two had a reduction in seizure frequency. No changes were seen in the children and adults receiving placebo^{88,89}. The supplementation with vitamin E reduced mean seizure frequency in a group of severely mentally handicapped patients with treatment resistance epilepsy. However, information was omitted regarding the dosage regimen and the response in

the placebo group⁹⁰. In a study of severely handicapped epileptic patients (ages 4-23 years) receiving anticonvulsants, supplementation with 100 IU/day alpha-tocopheryl acetate for one month had no effect on seizure frequency⁸³. The teenagers and adults with uncontrolled epilepsy were randomly assigned to receive, in double-blind fashion, 600 IU/day vitamin E or placebo for three months. The mean seizure frequency decreased by 25.7 percent during the placebo period and by 13.8 percent during the vitamin E period compared with baseline⁸⁵. Although the research on efficacy is conflicting, vitamin E is relatively safe and may be considered for adjunctive treatment in epileptic patients, particularly children.

3.5 Vitamin K: The incidence of vitamin K deficiency is increased in neonates of mothers receiving enzyme-inducing antiepileptic drugs and vitamin K1 treatment decreases the frequency of vitamin K deficiency in these neonates⁹¹. 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 20 mg/day vitamin K1 for two weeks before delivery. No hemorrhages occurred in the babies and prothrombin times were all normal at birth. This study suggested that vitamin K1 should be given routinely to drug-treated epileptic women near the end of pregnancy⁹².

4. Discussion

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 AEDs⁹³.

Linolenic acid prevents kainate-induced seizures and neuronal death and has neuroprotective effects^{94,95}, supplementation with fish oil, providing omega-3 fatty acids, reduced seizure frequency, but the beneficial effect was not sustained thereafter. Health care professionals 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 reasonable⁹⁶⁻¹⁰⁰. Of course, cost-benefit ratio should always be considered and over consumption of vitamin supplements should be avoided. The pyridoxine, folic acid, and biotin supplementation is necessary in patients with pyridoxin, cerebral folate deficiency, or biotinidase deficiency, respectively, there is no evidence to support their use in other circumstances, to control the seizures. In addition, though evidence is lacking, the use of high dose of folic acid supplements in women with epilepsy before conception and during pregnancy, supplementation with vitamin D in patients taking enzyme-inducing antiepileptic drugs and valproate, and finally, vitamin K in pregnant women taking antiepileptic drugs and their newborns are recommended¹⁰¹⁻¹⁰⁵. The relation between other nutrients (e.g., vitamin E and Omega-3 fatty acids and seizures) should be investigated further before asserting any recommendations. On the other hand, unnecessary and excessive vitamin and mineral supplementation may actually be harmful (106-108). For many people with epilepsy a healthy, balanced diet is the best, but many patients have nutritional deficiencies. In one recent study, at least 30% of children with intractable epilepsy had intakes below the recommended dietary allowance for vitamins D, E, and K, folate, calcium, and linoleic acid¹⁰⁹⁻¹¹².

5. Conclusion

A number of 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 anticonvulsant drugs. In most cases, nutritional therapy is not a substitute for anticonvulsant medications. However, in selected cases, depending on the effectiveness of the interventions, dosage reductions or discontinuation of medications may be possible. Because much of the research on epilepsy management with diet, nutrients, and hormones is preliminary.

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