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The information contained herein includes both psychological and non psychological interventions. The delivery of psychological services requires a medical referral whilst non psychological services do not.

Each person is an individual and has a unique psychological profile, biochemistry, developmental and social history. As such, advice will not be given over the internet and recommendations and interventions within this website cannot be taken as a substitute for a thorough medical or allied health professional assessment or diagnosis.

Nutritional Depletion as a Side Effect of Anticonvulsant Medications

Article QUICK LINKS :

INTRODUCTION

Anticonvulsant medications such as barbiturates, phenytoin, carbamazapine, primidone, and valporic acid are known to deplete vital nutrients. Each of these is outlined below along with the vitamins and minerals they are known to deplete.

- **Barbiturates:** Such as Phenobarbitol or Phenobarbitone can cause depletion of calcium, folic acid, vitamin D, vitamin K, and biotin.
- **Phenytoin:** Such as Dilantin can deplete a wide range of nutrients including biotin, calcium, folic acid, vitamin B1, vitamin B12, vitamin D and vitamin K.
- **Carbamazepines:** Such as Tegratol, Teril, Carbium can deplete biotin, folic acid and vitamin D.
- **Primidone:** In Mysoline can deplete folic acid and biotin.
- **Valporic Acid:** In Epilim and Valpro can cause depletion of folic acid, carnitine, copper, selenium and zinc.

HEALTH IMPLICATIONS AS A RESULT OF NUTRIENT DEPLETION/ DEFICIENY DUE TO ANTICONVULSANTS

VITAMIN B1 (Thiamine)

B vitamims act as coenzymes, helping enzymes to perform their function properly. The B vitamins help to maintain the health of nerves, skin, eyes, hair, liver and mouth as well as healthy muscle tone in the gastrointestinal tract and proper brain function. Only those B vitamins depleted by anticonvulsant medications will be mentioned here.

Thiamine enhances circulation and assists in blood formation, carbohydrate metabolism, and the production of hydrochloric acid (needed for proper digestion). Thiamine also optimises cognitive activity and brain function and is needed for proper muscle tone of the intestines, stomach and heart. Thiamine also acts an antioxidant protecting the body from the degenerative effects of aging, alcohol consumption and smoking. A vitamin B1 deficiency results in beriberi, constipation, edema, enlarged liver, fatigue, forgetfulness,

gastrointestinal disturbances, heart changes, irritability, laboured breathing, loss of appetite, muscle atrophy, nervousness, numbness of the hands and feet, pain and sensitivity, poor coordination, tingling sensations, weak and sore muscles, general weakness, and severe weight loss.

Blood levels are low in epileptics possibly due to ingestion of anticonvulsants (Krause). Moreover, thiamine deficiency may provoke seizures in predisposed patients (Keyser). It is interesting to note in a double blind crossover study patients who had been on phenytoin alone or in combination with phenobarbital for several years received 50 mg of thiamine daily. After 6 months thiamine, improved the neuropsychological functions in both verbal and non verbal IQ testing were noted (Botez).

VITAMIN B12 (Cyanocobalamin)

Vitamin B12 is needed to prevent anaemia. It aids folic acid in regulating the formation of red blood cells and helps in the utilisation of iron. This vitamin is also required for adequate digestion, absorption of foods, the synthesis of protein, and the metabolism of carbohydrates and fats. It helps cell formation and cellular longevity. Additionally, vitamin B12 prevents nerve damage, maintains fertility and promotes growth and development by maintaining the fatty sheaths that cover and protect nerve endings. Vitamin B12 is used in the production of acetylcholine, a neurotransmitter that assists learning and memory. It also enhances sleep patterns, allowing for a more restful and refreshing sleep. A deficiency of vitamin B12 can be caused by malabsorption, which is common in digestive disorders. Deficiency can cause abnormal gait, bone loss, chronic fatigue, constipation, depression, digestive disorders, dizziness, drowsiness, enlargement of the liver, eye disorders, hallucinations, headaches (including migraines), inflammation of the tongue, irritability, laboured breathing, memory loss, moodiness, nervousness, neurological damage, palpitations, pernicious anaemia, ringing in the ears (tinnitus), and spinal cord degeneration. Epileptics on anticonvulsant medication demonstrate reduction in serum vit B12 levels (Rosciszewzka).

VITAMIN B6

High dose pyroxidine may benefit patients with recurrent seizures due to acute infectious diseases. In one study of 40 infants and children total response rates in the pyroxidine and control groups were 92.5% and 64% respectively. A highly significant difference. Seizures resolved after around a day in the pyroxidine group and after three days in the control group. No adverse effects of pyroxidine were apparent in the observation period (Jiao, Baumeister & Eggar J).

It is important to note that B vitamins should never be given in isolation and a potent B complex should always be given when single B vitamins are indicated.

FOLIC ACID (Pteroylglutamic acid- PGA)

Folic acid is considered a brain food and is needed for energy production and the formation of red blood cells. I also strengthens immunity by assisting in the proper formation and functioning of white blood cells. If functions as a coenzyme in DNA and RNA synthesis and is necessary for healthy cell division and replication. All anticonvulsant drugs deplete folic acid. In women, this can lead to serious health problems. A deficiency in folic acid disrupts DNA and RNA metabolism, thus producing abnormal cells. This problem is particularly acute in cells with the most rapid turnover- red blood cells, leukocytes, and epithelial cells of the stomach, intestine, vagina, and uterine cervix. There is a higher need for folic acid during pregnancy and this deficiency is associated with birth defects such as spina bifida. Folic acid deficiency can cause anemia, cervical dysplasia (leading to hysterectomies), headaches, fatigue, depression, hair loss, growth impairment, anorexia, insomnia, diarrhea, nausea, apathy, memory loss, paranoia, increased infections and elevated homocysteine levels. Elevated homocysteine levels is now recognised as a serious independent risk factor for atherosclerosis (hardening of the arteries due to the accumulation of fatty plaques). Even moderate levels of homocysteine substantially increase the risk for plaque build-up and blood clots. Folic acid is needed with adequate amounts of vitamin B6 and B12 to convert homocysteine to non-harmful amino acids in the body. A folic acid deficiency is also associated with increased risk of developing breast cancer and colorectal cancer.

Folate metabolism is intimately involved in the epileptogenic process. Experimentally induced seizures deplete brain folate as do anticonvulsants (Smith). It should be noted that results of studies investigating the effects of folate supplementation on seizures have been mixed.

BIOTIN

Biotin aids in cells growth; fatty acid production; in the metabolism of carbohydrates, fats and proteins and in the utilisation of the other B-complex vitamins. It also promotes healthy sweat glands, nerve tissue, and bone marrow. In addition it also helps to relieve muscle pain. Biotin deficiency can result in hair loss, depression, anaemia, insomnia, loss of appetite, muscular pain, nausea, soreness of the tongue, inflammation or pallor of the skin and mucous membranes, and an elevation of blood glucose and cholesterol levels. Biotin deficiency is frequently associated with epileptic seizures and studies suggest that it falicitates convulsive disorders (Bregola). Treatment with anticonvulsants appears to increase biotin catabolism (breakdown). Over time this can lead to reduced biotin status (Mock). Biotin repletion should be considered in an infant or child with unexplained seizure and a trial of biotin should be considered for infants less than one year of age with poorly controlled seizures (Salbert).

CARNITINE

Although considered an amino acid, carnitine is more related to the B vitamins. Unlike true amino acids, carnitine is not used for protein synthesis or a neurotransmitter. Its main function in the body is to facilitate the transport of long-chain fatty acids to the mitochondria where they are burned to provide energy. This is a major source of energy for the muscles. Studies have shown decreased carnitine levels in people suffering from chronic fatigue syndrome. Carnitine works with the antioxidants vitamins C and E to help slow the aging process by promoting the production of acetyl-transferase, an enzyme in the mitochondria of brain cells that is vital for the production of cellular energy there. Unless there is an inherited defect in carnitine synthesis, the body normally makes adequate levels of carnitine provided there are sufficient amounts of iron, vitamin B1, vitamin B6, vitamin C and the amino acids lysine and methionine available. Administration of valporic acid (Epilim) can create a carnitine deficiency, which can cause fatigue, confusion, muscle weakness, cramps, heart pain and obesity. Numerous studies have found that patients taking anticonvulsant medications particularly Epilim have lower plasma levels than controls (Coulter). Furthermore, carnitine deficiency seems to be related to the duration of treatment (Chung).

CALCIUM

Since anticonvulsant medications decrease the intestinal absorption of calcium, individuals taking these medications are at increased risk of developing a calcium deficiency. Simple calcium supplementation will not solve this problem because the calcium deficiency is the result of a vitamin D deficiency, and vitamin D is necessary for calcium absorption. Vitamin D supplementation is therefore necessary to increase the absorption of calcium. The well known results of calcium deficiency are skeletal problems such as rickets (softening and bending of the bones) in children and osteoporosis (porous, brittle bones) or osteomalacia in adults. Additionally, calcium deficiency can lead to high blood pressure, muscle cramps, heart palpitations, tooth decay, back and leg pains, insomnia, and nervous disorders. During idiopathic generalised tonic-clonic seizures, serum and cerebrospinal fluid calcium levels are elevated (Sood).Anticonvulsants interfere with calcium metabolism in a poorly understood manner causing depressed blood calcium levels. Occasionally, rickets or osteomalacia may develop (Flodin).

MAGNESIUM

Magnesium is needed in over 300 chemical reactions in the body and depletion is known to cause marked irritability in the central nervous system which eventually results in seizures. Low levels correlate with increased frequency, poor control and longer duration of seizures. Status epilepticus and EEG abnormalities are also related to low cerebral spinal fluid magnesium levels. Additionally, there is a negative correlation between the serum magnesium level and severity of the epilepsy, with the lowest levels seen in status epilepticus. Moreover, 29 out of 30 epileptic children with grand mal or petit mal seizures who received magnesium and stopped their anticonvulsants showed marked improvement (Barnet). Magnesium is a natural calcium channel blocker and it is known that serum calcium and CSF levels may be elevated and remain so for at least 24 hours. Supplementation with magnesium to correct the deficiency is therefore clearly indicated.

VITAMIN C

Vitamin C is a one of the antioxidants needed by all cells in the body. Anticonvulsant therapy seems to have a negative influence on plasma levels of vitamin C (Singh). Lower vitamin C levels are associated with poor results in tests of central and peripheral nervous system function including cerebellar disturbances. Both males and females with lower Vit C levels showed a tendency toward macrocytic anemia. (Krause).

VITAMIN E

Vitamin E (d alpha tocopherol) is a powerful antioxidant that prevents the perioxidation of lipids in the cell membranes. Epileptics on anticonvulsant medications may have reduced plasma alpha tocopherol (Vitamin E) levels and this may be due in part to the use of anticonvulsants. Under double blind conditions vitamin E supplementation has been shown to reduce seizures. In one double blind study of 24 epileptic children with refractory epilepsy, after 3 months 83% of the 12 treated children had a greater than 60% reduction in seizures (and half of these children had 90 to 100% reduction) compared to none of the controls. When the controls were switched to 70 to 100% in all of them (Ogunmekan, Krause).

VITAMIN D

Vitamin D deficiency can cause skeletal problems because not enough calcium phosphate is deposited in the bone matrix. In children, the bones are not strong enough to withstand the ordinary stresses of weight-bearing, which can result in muscle weakness, pain, knock-knees, bowed legs, spinal curvature, pigeon breast, disfiguring of the skull, and tooth decay and dental problems. In adults, it leads to osterporosis. As a result of anticonvulsant treatment, serum levels of both 25-hydroxy vitamin D and 1, 25 - dihydroxy Vitamin D (active vitamin D3) may be depressed (Valimaki). Marked elevation of serum alkaline phosphatase particularly when in concert with hypercalcemia would suggest anticonvulsant induced bone disease (Alderman)

VITAMIN K

Vitamin K is needed for the production of prothrombin, which is a necessary for blood coagulation. Recent research indicates that vitamin K is also necessary for bone formation and repair because it is necessary for the synthesis of osteocalin, the protein in bone tissue on which calcium crystallizes. It also plays an important role in the intestines and helps to convert glucose into glycogen for storage in the liver. It is also thought to increase resistance to infection in children and help prevent cancers that target the inner linings of the organs. Since Vitamin K regulates blood clotting mechanisms, a deficiency can lead to coagulation problems resulting in bleeding and hemorrhage in internal organs and a disruption in normal bone growth and repair. The majority of this vitamin's supply is synthesised in the body by the "friendly" bacteria normally present in the intestine. Hence probiotics are important for anyone on anticonvulsant medications, particularly those on Phenobarbitol and Dilantin.

COPPER
Among its many functions, copper aids in the formation of bone, haemoglobin and red blood cells, and works in conjunction with zinc and vitamin C to form elastin, an important skin protein. Additionally, it is essential for the formation of collagen (protein) used in bones, skin and connective tissue. It is involved in the healing process, energy production, hair and skin colouring and taste sensitivity. A copper deficiency can lead to anemia, baldness, diarrhea, general weakness, elevated levels of serum cholesterol, impaired respiratory function and skin sores. Seizures can be caused by copper deficiency (Sorensen 1979), however, serum copper and ceruloplasmin concentrations are often elevated. These findings appear to be partly due to the effects of anticonvulsants, perhaps due to hepatic (liver) enzyme induction (Motta).

SELENIUM
Selenium is a vital antioxidant, especially when combined with vitamin E. It protects the immune system by preventing the formation of free radicals that can damage the body. It's principal function is to inhibit the oxidation of lipids (fats) as a component on the enzyme glutathione peroxidase. It also plays an important role in regulating the effects of the thyroid hormone on fat metabolism. Selenium and vitamin E act synergystically to aid in the production of antibodies and to help maintain a healthy heart and liver. This trace element is needed for pancreatic function and tissue elasticity. Research has also indicated that it prevents the formation of certain types of tumours (lung, prostrate, colorectal). Selenium deficiency has been linked to cancer and heart disease. It is also associated with exhaustion, growth impairment, high cholesterol levels, infections, liver impairments, pancreatic insufficiency, and sterility. Australian soils are notably deficient in selenium.

Studies suggest that brain selenium depletion may trigger seizures and subsequent neural damage due to selenium's important role in the defence of neuronal cells against oxygen radical formation and peroxidative processes (Calomme, Ramakers, Webber).

ZINC
Zinc is an important mineral for a healthy immune system. It is required for protein synthesis and collagen formation and promotes the healing of wounds. It is a constituent of insulin and many vital enzymes. Sufficient intake and absorption of zinc is vital to maintain the proper concentration of vitamin E in the blood. Zinc also prevents acne and regulates the oil glands; allows for the acuity of taste and smell; protects the liver from chemical damage; and is vital for bone formation. A zinc deficiency may result in a loss of the senses of taste and smell, cause fingernails to become thin, peel and develop white spots. Other signs of a zinc deficiency include acne, hair loss, growth impairment, delayed sexual maturation, fatigue, high cholesterol levels, impaired night vision, impotence, increased susceptibility to infection, infertility, memory impairment, a propensity to diabetes, prostrate problems, recurrent colds and flu, skin lesions and slow wound healing.

Zinc deficiency is known to cause seizures (Prasad). Anticonvulsants can cause zinc deficiency either by reducing zinc absorption in the gut through chelation or by causing diarrhoea (Lewis-Jones). Studies on zinc supplementation suggest zinc ions limit the excitatory response in the dentate granule cells of patients with medial temporal epilepsy (Williamson). Furthermore, zinc supplementation has been shown to protect against the development of seizures, suggesting that zinc may be an essential component of a natural, anticonvulsant tissue response to abnormal excitation (Sterman). Australian soils are notably deficient in zinc.

A plethora of vitamin supplements is available over-the counter in health food shops in Australia. However, they come in various forms, combinations and amounts and many do not deliver what they promise. They are available in tablet, capsule, gel-capsule, powder, sublingual, lozenge and liquid forms. Some can also be administered by injection. How quickly they are absorbed and assimilated into the body (bio-availability) depends on the form they are in, whether they are synthetic (laboratory manufactured) or natural (nature's unprocessed food sources) and the ingredients used as fillers. It is highly unlikely that you will find one supplement or brand to cater for all of your needs. For this reason, caution is suggested when buying over-the counter supplements and the need for qualified nutritional advice is paramount.

For more information or to make an appointment please contact us on (02) 9637 9998 during business hours.

REFERENCES

1. Aldreman CP, Hill CL (1994): "Abnormal bone mineral metabolism after long term anticonvulasnt treatment. Ann Pharmocother 28 (1): 47-8

2. Balch, P.A. & Balch, J.F., (2000): Prescriptions for Nutritional Healing (3rd edition), Avery Books, New York

3. Barnett, LB (1959) Journal of Clinical Physiology 1: 25.

4. Baumeister, FAM, Eggar J (1996): "Diagnosis and therapy of Vitamin B6 dependent epilepsy". Monatsschr Kinderheilkd 144: 534-5.

5. Botez MI et al (1993): "Thiamine and folate treatment of chronic epileptic patients: a controlled study with the Wechsler IQ Scale. Epilepsy Res 16 (2): 157-63.

6. Bregola, G et al (1996): "Biotin deficiency felicitates kindling hyperexcitability" Neuro Report 7 (11): 1745-8.

7. Calomme MR et al (1996): "Selenium deficiency triggering intractable seizures" Therapeutic Uses of Trace Elements Vol 62: 359-64

8. Coulter DL (1995): "Carnitine deficiency in Epilepsy: Risk factors and treatment". J Child Neurology 10 Suppl 2:S32-S39.

9. Chung S et al (1997): "Alerations in the carnitine metabolism in epileptic children treated with valporic acid". J Korean Med Sci. 12 (6): 553-8.

10. Flodin NW (1988): Pharmocology of Micronutrients. Alan R List, New York Inc.

11. Jiao FY et al (1997): "Randomised controlled trial of high dose intravenous pyridoxine in the tresatment of recurrent seizures in children". Pediatr Neurol 17 (1):54-7.

12. Kogan, VE et al (1983): "Role of lipid peroxidation in damage to serotonin receptors and development of epileptiform seizures during hypoxia". Biull Eksp Biol Med 96 (12) 16-18.

13. Kovalenko, VM et al (1984): "Alpha tocopherol in the complex treatment of several forms of epilepsy". Zh Neuropathol Psikhitv (in Russian) 6: 892-7.

14. Krause KH et al (1982): "Reduction of biotin level as a possible factor in the mode of action of anticonvulsants". Arch Psychiatr Nervenkr . 23 (2):141-8 (in German).

15. Krause KH et al (1986): "B vitamins in Epileptics". Bibl Nutr Dieta. 38:154-67

16. Krause KH et al (1988): "Effect of long term treatment with antiepileptic drugs on the vitamin status". Drug Nutr Interact. 5 (4) 317-43.

17. Keyser A (1991): "Epileptic manifestations and vitamin B1 deficiency". Eur Neurol. 31:121-5.

18. Lewis-Jones MS et al (1985): "Cutaneous manifestations of zinc deficiency during treatment with anticonvulsants". BMJ 29-Z: 603-4.

19. Mock DM A, Dyken ME (1997): "Biotin catabolism is accelerated in adults receiveng long term therapy with anticonvulsants" Neurology 49 (5):1444-7.

20. Motta E (1998): "Concentration of copper and ceruloplasmin in serum of patients treated for epilepsy" Wiad Lek 51 (3-4): 156-161 (in Polish).

21. Ogunmekan AO (1985): "Plasma vitamin E levels in normal children and in epileptic childrenwith and without anticonvulsant therapy: Trop Geog Med 37:175-7.

22. Ogunmekan AO, Hwang PA (1989): "A randomised double blind, placebo controlled, clinical trial of d-alpha tocopherol (vitamin E) as add-on therapy for epilepsy in children". Epilepsia 30 (1): 84-9.

23. Ramaekers VT (1994): "Selenium deficiency triggering intractable seizures". Neuro Pediatrics 25 (4):217-23.

24. Rosciszewzka D et al (1993): "Serum levels of vitamin B12 in epileptic patients treated with carbamazepine (Tegratol)". Neurol Neurochir Pol 27 (5) 671-5 (In Polish).

25. Singh RB et al (1995): "Dietary intake and plasma levels of antioxidant vitamins in health and disease: A hospital based case controlled study". J Nutr Environ Med 5: 235-42.

26. Sorrenson JRJ (1979): "Therapeutic uses of copper" Jo Nriagu Ed Copper in the Environment Part 2: Health Effects. John Wiley & Sons, New York.

27. Salbert BA et al (1993): "Characterisation od seizures associated with biotinidase deficiency". Neurology 43 (7):1351-5.

28. Smith DB, Obbens EAMT (1997): "Antifolate-antiepileptic" in Botez MI & Reynolds BH (Eds.) Folic acid in Neurology, Psychiatry amd Internal Medicine. Raven Press New York.

29. Sterman MB et al (1988): "Zinc and seizure mechanisms" in Nutritional Modualtion of Neural Function. J Morley & Sterman Eds 307-19. New York Academic Press.

30. Sood SK et al (1993): Serum, CSF, RBC and urinary levels of magnesium and calcium in idiopathic generalised tonic clonic seizures". Indian J Med Res 98: 152-4.

31. Pelton, R & LaValle (2000): The Nutritional Cost of Prescription Drugs- How to maintain good nutrition while using prescription drugs. P 24-40. Morton Publishing Company.

32. Prasad AS et al (1965): "Determination of Zinc in biological fluids by atomic absorption, spectrophotometry in normal and cirrhotic subjects". J Lab Clin Med 66:508-16.

33. Valakami MJ et al (1994): "Bone mineral density measured by dual energy Xray, absorptiometry and novel markers of bone formation and reabsorption in patients on antiepileptic drugs" J Bone Minr Res 9 (5): 631-7.

34. Webber GF et al (1991): "Glutathione peroxidase deficiency and childhood seizures". Lancet 337: 1443-4.

35. Werbach M R, MD (1999): Textbook of Nutritional Medicine. Third Line Press Inc. CA.

36. Williamson A, Spencer D (1995): "Zinc reduces dentate granule cell hyperexcitablity in epileptic humans". Neuro Report 6 (11): 1562-4.