Vitamin B_6 Related Epilepsy during Childhood

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In some patients without vitamin B_6 deficiency, epilepsy can not be controlled without an extra supplement of vitamin B_6. The therapeutic role of pyridoxal phosphate (PLP), the active form of vitamin B_6, may not be replaced with other forms of vitamin B_6 sometimes. Until now, four inborn errors of metabolism are known to affect vitamin B_6 concentrations in the brain. Three of them are hyperprolinemia type 2, antiquitin deficiency, and pyridoxine phosphate oxidase deficiency. The fourth disorder occurs in neonates with hypophosphatasia and congenital rickets. All patients with these conditions present with early-onset epilepsy that is resistant to conventional antiepileptic medications. Patients with three of the conditions respond to any form of vitamin B_6. Only those with pyridoxine phosphate oxidase deficiency respond to PLP instead of pyridoxine. Interestingly, the authors have successfully treated many patients without the above four disorders using vitamin B_6, and have found that the treatment was more effective with PLP than with pyridoxine, though the mechanism is not known. Since PLP is as inexpensive as pyridoxine, we suggest replacing PLP for pyridoxine when treating children with epilepsy. *(Chang Gung Med J 2007;30:396-401)*

Key words: Vitamin B_6, epilepsy, hypophosphatasia, pyridoxine phosphate oxidase, hyperprolinemia type II, pyridoxine-dependent epilepsy

Vitamin B_6 plays numerous roles in the human body. They include transamination of amino acids, decarboxylation reactions, modulation of the activity of steroid hormones, and regulation of gene expression. Vitamin B_6 deficiency may cause γ-aminobutyric acid (GABA) deficiency and seizures. If left untreated, it can lead to permanent neurological sequelae. Thus, it is important to know the normal mechanism for the metabolism of vitamin B_6, the role of alkaline phosphatases in the transportation of vitamin B_6 into the brain, and the disorders of the metabolism of vitamin B_6. Vitamin B_6 has long been used in many patients with epilepsy. Only a small proportion of patients have been confirmed to have a specific disorder in metabolizing vitamin B_6. Most of the remaining patients received vitamin B_6 as adjuvant to antiepileptic drugs. Some patients with epilepsy or specific epileptic syndromes such as infantile spasms were well controlled using ordinary or mega- dosage of vitamin B_6. Our recent experiences suggest that the active form of vitamin B_6 is better than the prototype. A proper treatment strategy for using vitamin B_6 in patients with epilepsy should be made.

Normal metabolism of vitamin B_6

Vitamin B_6 is a water soluble vitamin that is present in the body as six vitamers: the alcohol pyridoxine (pyridoxol), aldehyde pyridoxal, amine pyridoxamine, and their respective 5'-phosphorylated esters. Vitamin B_6 is ingested from the diet and is present in many kinds of food including meats, puls-

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es, cereals, vegetables and some fruits; a proportion of vitamin B_6 is derived from intestinal bacterial flora. Animal-derived vitamin B_6 consists mostly of phosphorylated pyridoxal and pyridoxamine while that from plants consists largely of free and bound pyridoxine.[1] Phosphorylated B_6 vitamers are converted to their free bases by intestinal alkaline phosphatases and these are then absorbed from the upper small intestine by a carrier-mediated system.[2] Absorption is rapid and the vitamers pass into the portal circulation and are taken up by the liver. Here, pyridoxine, pyridoxamine and pyridoxal are phosphorylated by pyridoxal kinase to their 5'-phosphate esters and pyridoxine phosphate and pyridoxamine phosphate oxidized by pyridox(am)ine phosphate oxidase (PNPO) to form pyridoxal phosphate (PLP). PLP is released from the liver into the circulation where it is bound by albumin and forms approximately 60% of circulating vitamin B_6 with lesser amounts of pyridoxine, pyridoxamine, and pyridoxal.

Only free vitamer bases can cross the blood brain barrier (BBB), mostly at the choroid plexi.[3] To penetrate through the BBB, PLP is cleaved to pyridoxal by non-specific membrane associated alkaline phosphatases and transported into cerebrospinal fluid (CSF) by an active transport mechanism that can also take up pyridoxine and pyridoxamine. Uptake of the free vitamers from CSF into brain cells is via a similar mechanism. Hypophosphatasia is a rare inherited metabolic disease characterized by rickets with reduced plasma and tissue alkaline phosphatase activity. It may be present during infancy, childhood, or adulthood. Various clinical manifestations reflect different forms of alkaline phosphatase gene expression. In one specific type of hypophosphatasia (MIM 171760), the defective transport of vitamin B_6 causes complicated seizures which respond to vitamin B_6 but are resistant to all antiepileptics.[4,5]

In the brain cells, vitamin B_6 is then trapped after the pyridoxine kinase catalyze the phosphorylating reaction of the pyridoxal, pyridoxine, and pyridoxamine. Pyridoxine and pyridoxamine phosphate are then oxidized by PNPO to form PLP.[6] PLP has excellent electron sink properties that make it a versatile organic catalyst. Except for glycogen phosphorylase, all enzymes that use PLP as a cofactor act upon amino acids or amines. The aldehyde group of PLP can undergo a Schiff base reaction with free amine groups to form an aldimine double bond linking the amino acids to the electron sinks. The unique environment produced by the enzymes determine the catalytic properties and the types and specificity of the holoenzyme.[7] More than 100 apoenzymes are known to require PLP as a cofactor and the holoenzymes catalyze diverse reaction specificities such as transamination, decarboxylation, racemisation, elimination and replacement reactions.

In the brain, PLP-dependent enzymes are involved in the metabolism of many amino acid and amine neurotransmitters such as dopamine, serotonin, glutamate, glycine, GABA, D-serine and taurine. They are also important in the synthesis of neuroprotective compounds such as kynurenic acid. Thus defects in the metabolism of PLP would be expected to cause major neurological consequences, such as vitamin B_6 deficiencies have long been known to induce epilepsy in human infants.[8]

Inborn metabolic disorders of vitamin B_6

Until now, in addition to hypophosphatasia (MIM 171760), three other disorders are known to cause defective vitamin B_6 metabolism. The first is PNPO deficiency, which causes pyridoxine nonresponsive, PLP-responsive neonatal epileptic encephalopathy.[9] The second is type II hyperprolinemia, which can cause pyridoxine responsive epilepsy.[10] The accumulation of pyrroline-5-carboxylic acid resulting in inactivation and finally a picture of PLP deficiency.[11] The third is pyridoxine dependent epilepsy (PDE), which has long been considered as an inborn error of vitamin B_6 metabolism or transport.[12] However, it was recently discovered that the deficiency of α-aminoadipic semialdehyde dehydrogenase may also cause inactivation of PLP.[13] It is important that the PNPO deficiency and PDE have been confirmed in their respective genetic defects during recent years.

Pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency (OMIM 610090)

To date, only five patients have been reported to have had PNPO deficiency.[9] One other case reported by the authors had pyridoxine nonresponsive, PLP responsive epilepsy though there was no evidence of PNPO in that patient.[14] The infants were born prematurely with evidence of fetal distress and had impaired postnatal adaptation resembling hypoxic-ischemic neonatal encephalopathy. Seizures devel-

oped during the first 12 hours of life and were resistant to conventional antiepileptic medications. Multiple seizure types developed and electroencephalogram (EEG) evolved to a burst-suppression pattern. There were no (or an incomplete) responses to intravenous pyridoxine supplements. However, two of the infants (including ours) responded promptly to PLP in a dose of 10 mg/kg given every 6 hours.[15] This response might be associated with initial severe cerebral depression like that seen in a proportion of cases with PDE.[9]

All five patients with PNPO deficiency in the same series had characteristic biochemical findings in the CSF, plasma and urine that were explicable as a block in metabolic pathways caused by deficiency of a PLP dependent enzyme.[9] In the CSF, there were reduced homovanillic and 5-hydroxyindoleacetic acids and raised 3-methoxytyrosine concentrations, raised glycine and threonine concentrations. Similar, but more variable changes were found in plasma. Urine showed increased excretion of vanillactic acid.

Type II hyperprolinemia (OMIM 239510)

Two types of hyperprolinemia appear to exist. In hyperprolinemia type I (OMIM 239500), the defect involves the enzyme proline oxidase. Mental retardation is not a feature. In hyperprolinemia type II, which is usually characterized by mental retardation and convulsions, the enzyme defect involves Δ^1-pyrroline-5-carboxylate dehydrogenase (P5CDH) due to mutation in the P5CDH gene. The P5CDH is a mitochondrial matrix NAD(+)-dependent dehydrogenase which catalyzes the second step of the proline degradation pathway, converting pyrroline-5-carboxylate (P5C) to glutamate. P5CDH deficiency causes the accumulation of proline and P5C in plasma and excessive excretion of P5C in urine.[16] P5C and PLP combine through a Claisen condensation or Knoevenengal type of reaction of the activated C-4 carbon of the P5C pyrroline ring with the aldehyde carbon of PLP. PLP is thus consumed and de-activated.[11] Generalized seizures occurred in approximately half of the affected patients with type II hyperprolinemia.[17] One child with type II hyperprolinemia developed seizures and patient with encephalopathy associated with pneumonia was found to be PLP deficient.[10] The seizures responded to pyridoxine 50 mg/day orally.

Pyridoxine-dependent epilepsy (PDE) (MIM 266100)

Pyridoxine-dependent epilepsy (PDE) has been known since 1954.[18] However, it is rare with an incidence of around one in 400000 births.[19] Patients with PDE are classified into the early-onset, typical group presenting within the first few days of life, and later onset, atypical group presenting up to 3 years of age.[20] Patients in the early-onset group may develop prenatal seizures from around 20 weeks of gestation. One third of the patients have neonatal encephalopathy with hyper-alertness, irritability and stimulus sensitive startle. This may be accompanied by systemic features such as respiratory distress, abdominal distension and vomiting, as well as metabolic acidosis. Multiple seizure types start within the first few days of life and are resistant to conventional antiepileptics. There may be structural brain anomalies such as hypoplasia of the posterior part of the corpus callosum, cerebellar hypoplasia or hydrocephalus, and other cerebral complications such as cerebral hemorrhage or white matter abnormalities.[21] The seizure activity is promptly (within minutes) responsive to 100 mg pyridoxine given intravenously. However, it has been reported that cerebral depression occurred after the first dose of pyridoxine in about 20% of infants with PDE. Usually the infants become hypotonic and sleep for several hours. Apnea, cardiovascular instability and isoelectric EEG rarely occur. Cerebral depression often occurs in infants who are also taking antiepileptics. Interestingly, the authors never had this kind of complication when using vitamin B_6 in hundreds of children with epilepsy.

In contrast, encephalopathy and brain structural anomalies were not noted in the group with late-onset PDE. Seizures may start anytime up to 3 years of age.[22] Often the seizures occur in the context of a febrile illness which may develop into status epilepticus. There is usually an initial response to conventional anti-epileptic drugs, however, the effects fade with time. Pyridoxine in a dose of 100 mg/day orally usually control the seizure activity within 1 to 2 days. Cerebral depression is not a complication of late-onset PDE.

The only way to confirm a diagnosis of PDE was to withdraw pyridoxine and demonstrate the recurrence of seizures that again showed prompt response to pyridoxine. The treatment is life long and the dose of pyridoxine used is usually around 15

mg/kg/day, and may be up to 500 mg/day. Learning difficulties, particularly language learning skills, seem to be a common complication of early-onset PDE.[21] Delay in the treatment of these patients over months or years causes severe motor disorders with learning difficulties and sensory impairment. It has been suggested that every neonate with seizures, even if perinatal asphyxia or sepsis is suspected, should be given a trial of intravenous vitamin B_6. Similarly, each child with the onset of epilepsy under 3 years of age should also be given a trial of oral vitamin B_6.[22]

Recently, it was shown that the mutation of the aldehyde dehydrogenase (ALDH) 7A1 gene, which is located on chromosome 5q31, is the most common cause of PDE. ALDH 7A1 gene encoding antiquitin, have been shown to abolish the activity of antiquitin as an α-aminoadipic semialdehyde dehydrogenase which results in the accumulation of L-Δ^1-piperideine-6-carboxylate (P6C).[13] α-Aminoadipic semialdehyde dehydrogenase is part of the pipecolic pathway of lysine catabolism. P6C has been shown to condense with PLP and to presumably inactivate it, causing PLP deficiency in brain.[13]

Which is better: pyridoxine or PLP?

In clinical practice, particularly in Taiwan and Japan, pyridoxine and PLP have been used as antiepileptic medications for patients with infantile spasms and childhood generalized and focal epilepsy. In the authors' series, 94 children with ages ranging from 8 months to 15 years were noted to have intractable idiopathic epilepsy (both partial and generalized seizures). Ten percents of the patients responded to PLP.[23] Of these, half responded to pyridoxine as well. The authors prefer using PLP as the first choice in some children with intractable epilepsy since the seizures responding to pyridoxine respond to PLP too, but not vice versa, in addition PLP is as inexpensive as pyridoxine.

REFERENCES

1. McCormick DB. Two interconnected B vitamins: riboflavin and pyridoxine. Physiol Rev 1989;69:1170-98.
2. Said HM. Recent advances in carrier-mediated intestinal absorption of water-soluble vitamins. Annu Rev Physiol 2004;66:419-46.
3. Spector R, Greenwald LL. Transport and metabolism of vitamin B6 in rabbit brain and choroid plexus. J Biol Chem 1978;253:2373-9.
4. Nunes ML, Mugnol F, Bica I, Fiori RM. Pyridoxine-dependent seizures associated with hypophosphatasia in a newborn. J Child Neurology 2002;17:222-4.
5. Yamamoto H, Sasamoto Y, Miyamoto Y, Murakami H, Kamiyama N. A successful treatment with pyridoxal phosphate for West syndrome in hypophosphatasia. Pediatr Neurol 2004;30:216-8.
6. Kang JH, Hong ML, Kim DW, Park J, Kang TC, Won MH, Baek NI, Moon BJ, Choi SY, Kwon OS. Genomic organization, tissue distribution and deletion mutation of human pyridoxine 5'-phosphate oxidase. Eur J Biochem 2004;271:2452-61.
7. John RA. Pyridoxal phosphate-dependent enzymes. Biochim Biophys Acta 1995;1248:81-96.
8. Coursin DB. Convulsive seizures in infants with a pyridoxine deficient diet. JAMA 1954;154:406-8.
9. Mills PB, Surtees RA, Champion MP, Beesley CE, Dalton N, Scambler PJ, Heales A, Briddon A, Scheimberg I, Hoffmann GF, Zschocke J, Clayton PT. Neonatal epileptic encephalopathy caused by mutations in the PNPO gene encoding pyridox(am)ine 5'-phosphate oxidase. Hum Mol Genet 2005;14:1077-86.
10. Walker V, Mills GA, Peters SA, Merton WL. Fits, pyridoxine, and hyperprolinaemia type II. Arch Dis Child 2000;82:236-7.
11. Farrant RD, Walker V, Mills GA, Mellor JM, Langley GJ. Pyridoxal phosphate de-activation by pyrroline-5-carboxylic acid. Increased risk of vitamin B6 deficiency and seizures in hyperprolinemia type II. J Biol Chem 2001;276:15107-16.
12. Baxter P. Pyridoxine-dependent seizures: a clinical and biochemical conundrum. Biochim Biophys Acta 2003;1647:36-41.
13. Mills PB, Struys E, Jakobs C, Plecko B, Baxter P, Baumgartner M, Willemsen MA, Omran H, Tacke U, Uhlenberg B, Weschke B, Clayton PT. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med 2006;12:307-9.
14. Kuo MF, Wang HS. Pyridoxal phosphate-responsive epilepsy with resistance to pyridoxine. Pediatr Neurol 2002;26:146-7.
15. Clayton PT, Surtees RA, DeVile C, Hyland K, Heales SJ. Neonatal epileptic encephalopathy. Lancet 2003;361:1614.
16. Phang JM, Hu CA, Valle D. Disorders of proline and hydroxyproline metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Childs B, Kinzler KW, eds. The Metabolic and Molecular Bases of Inherited Disease. 7th ed. New York: McGraw-Hill, 2001:1821-38.
17. Flynn MP, Martin MC, Moore PT, Stafford JA, Fleming GA, Phang JM. Type II hyperprolinaemia in a pedigree of Irish travellers (nomads). Arch Dis Child 1989;64:1699-707.

18. Hunt AD Jr, Stokes J Jr, McCrory WW, Stroud HH. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. Pediatrics 1954;13:140-5.
19. Been JV, Bok LA, Andriessen P, Renier WO. Epidemiology of pyridoxine dependent seizures in the Netherlands. Arch Dis Child 2005;90:1293-6.
20. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child 1999;81:431-3.
21. Baxter P, Griffiths P, Kelly T, Gardner-Medwin D. Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. Dev Med Child Neurol 1996;38:998-1006.
22. Chou ML, Wang HS, Hung PC, Sun PC, Huang SC. Late onset pyridoxine-dependent seizures: report of two cases. Acta Paediatr Taiwan 1995;36:434-8.
23. Wang HS, Kuo MF, Chou ML, Hung PC, Lin KL, Hsieh MY, Chang MY. Pyridoxal phosphate is better than pyridoxine for controlling idiopathic intractable epilepsy. Arch Dis Child 2005;90:512-5.

維他命 B_6 相關的兒童癲癇症

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一些不是維他命 B_6 缺乏的病童，他們的癲癇卻要額外補充維他命 B_6 才能控制，有時在治療上，活性的維他命 B_6 —pyridoxal phosphate (PLP) 又非其他型式的維他命 B_6 可以取代。截至目前爲止，已知四種先天代謝異常會影響腦中的維他命 B_6 濃度，其中三者分別是：第二型的 hyperprolinemia，antiquitin 缺乏症，及 pyridoxine phosphate oxidase (PNPO) 缺乏症，第四者則是發生於新生兒的 hypophosphatasia 併先天佝僂症，所有這些病人都在嬰兒早期就出現傳統抗癲癇藥控制不了的癲癇，其中三種的癲癇可以使用所有型式的維他命控制，唯獨 PNPO 缺乏症只對 PLP 有所反應，其他型式的維他命 B_6 均不行。有趣的是，我們以 PLP 治療了不少非以上四者的癲癇病童，他們用其他型式的維他命 B_6 療效不佳。雖然作用機轉未明，但 PLP 和一般維他命 B_6 一樣不貴，我們建議全面以 PLP 取代其他維他命 B_6 治療癲癇病童。(長庚醫誌 2007;30:396-401)

關鍵詞：維他命 B_6，癲癇，hypophosphatasia，pyridoxine phosphate oxidase，第二型的 hyperprolinemia，維他命 B_6 依賴型癲癇

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