Epilepsy & Behavior 52 (2015) 154–158

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Pyridoxine deficiency in adult patients with status epilepticus☆

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ARTICLE INFO

Article history:
Received 16 July 2015
Accepted 12 August 2015
Available online 28 September 2015

Keywords:
Pyridoxine deficiency
Vitamin B6 deficiency
Status epilepticus
Epilepsy
Adult

ABSTRACT

An 8-year-old girl treated at our facility for superrefractory status epilepticus was found to have a low pyridoxine level at 5 μg/L. After starting pyridoxine supplementation, improvement in the EEG for a 24-hour period was seen. We decided to look at the pyridoxine levels in adult patients admitted with status epilepticus. We reviewed the records on patients admitted to the neurological ICU for status epilepticus (SE). Eighty-one adult patients were identified with documented pyridoxine levels. For comparison purposes, we looked at pyridoxine levels in outpatients with epilepsy (n = 132). Reported normal pyridoxine range is >10 ng/mL. All but six patients admitted for SE had low normal or undetectable pyridoxine levels. A selective pyridoxine deficiency was seen in 94% of patients with status epilepticus (compared to 39.4% in the outpatients) which leads us to believe that there is a relationship between status epilepticus and pyridoxine levels.

1. Introduction

An 8-year-old girl admitted for status epilepticus had seizures refractory to multiple AED's, VNS placement, ketamine infusion, and propofol infusion. She had a low pyridoxine level of 5 ng/mL. An improvement in the EEG was seen within 24 h after starting pyridoxine supplementation. The patient died of complications secondary to hypothermia protocol and metabolic acidosis. In light of her short but impressive response to pyridoxine, we decided to look at pyridoxine levels in our adult patients with status epilepticus (SE).

2. Methods

We obtained IRB approval to evaluate our patients admitted to the Ochsner Medical Center, Jefferson Campus, neurological ICU for SE. The patients were admitted between January 2014 and February 2015. Eighty-one adult patients with SE were identified with documented pyridoxine levels. For comparison purposes, we looked at serum pyridoxine levels in outpatients with epilepsy from the past three years (n = 132). A level of 10 ng/mL and below was chosen as a low pyridoxine level.

3. Results

Upon review of the data, all but six of the patients admitted for SE had low levels of pyridoxine of which seventeen patients had undetectable levels. When this was compared to the outpatient population, a larger proportion of patients (n = 80) had normal levels of pyridoxine. None of the patients in the outpatient group had undetectable levels. The mean pyridoxine was 4.7 ng/ml in the group with status epilepticus and 25.2 ng/ml in the outpatient group. This difference is statistically significant ($p < 0.0001$ using Fisher's exact test). See Figs. 1 and 2.

Fifty-one patients with pyridoxine deficiency had documented B vitamins. Fourteen patients were deficient in B1, 1 patient in B2, and 12 patients in B12. None of the patients were deficient in all four vitamin levels (B1, B2, B6, and B12).

4. Discussion

4.1. Pyridoxine

Albert Svent-Gyorgy first isolated pyridoxine in 1934 [1]. Pyridoxine is found in animal and plant-derived food [2]. The standard vitamin B6 supplement is pyridoxine hydrochloride (HCL) which is inexpensive. Pyridoxine is a water soluble vitamin and is absorbed by the upper small intestine. It is then transported to the liver where it is first oxidized to pyridoxal and then undergoes phosphorylation to pyridoxal 5′-phosphate (P5P) in the liver. The metabolic active coenzyme form of vitamin B6 is P5P. It binds albumin and is then transported to the tissue where it undergoes extracellular dephosphorylation to allow cellular uptake [1].

☆ This paper is part of the Special Issue based on The 5th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures (Volume 49).

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http://dx.doi.org/10.1016/j.yebeh.2015.08.015
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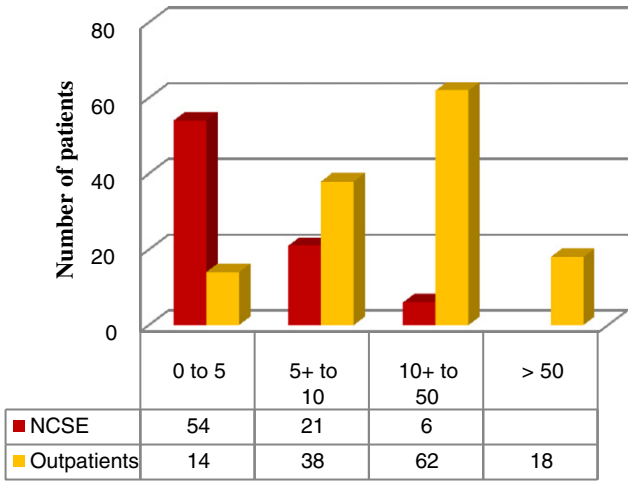

Fig. 1. Pyridoxine blood level (ng/ml) in patients with SE (n = 81) versus outpatients (n = 132).

P5P is vital in 140 metabolic reactions [2]. Pyridoxine has multiple functions including nitrogen/protein metabolism and heme synthesis. It is involved in the production of neurotransmitters and hormones, formation of keto acids, cleavage of glycogen, formation of heme precursors, phospholipid synthesis, and other enzyme reactions.

Pyridoxine has been used to treat anemia, carpal tunnel syndrome, premenstrual syndrome, hyperhomocysteinemia, and morning sickness. An adequate level of plasma pyridoxal 5′-phosphate >30 nmol/L [3]. Please note that 1 ng/ml of pyridoxine is equal to 4.046 nmol/L. Table 1 describes various methods of pyridoxine detection.

4.1.1. Pyridoxine deficiency

Classic pyridoxine deficiency syndrome presents with atrophic glossitis with ulceration, seborrheic dermatitis, angular cheilitis, conjunctivitis, intertrigo, neuropathy, confusion, and somnolence [2].

Those at risk of pyridoxine deficiency include the elderly, alcoholics, renal patients, liver patients, pregnant patients, and those with rheumatoid arthritis, type I diabetes, and HIV [2]. Pyridoxine deficiency can be iatrogenically induced with the introduction of the antituberculosis drug, isoniazid, and antiparkinsonian drug, carbidopa, or through the ingestion of ethylene glycol or monomethylhydrazine (e.g., *Gyromitra* mushroom) [4].

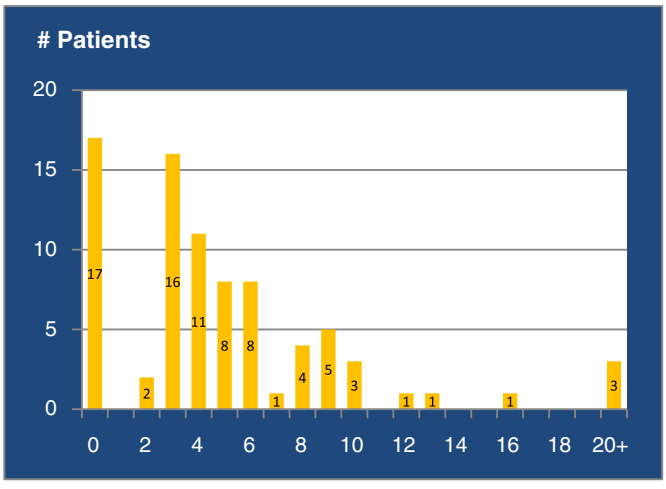

Fig. 2. Pyridoxine blood level (ng/ml) in patients with SE (n = 81).

Table 1
Available methods to measure pyridoxine levels.

Test for pyridoxine deficiency
• Activation coefficient for RBC aspartate aminotransferase • Urinary excretion of vitamin B_6 metabolite • Plasma pyridoxal phosphate (PLP) concentration — reflects tissue stores Deficiency levels < 10 ng/mL

4.1.2. Epilepsy and GABA/glutamate

In 1978, Laott studied the brain of a patient with epilepsy and found decreased levels of GABA as well as decreased white matter [5]. The active component, P5P, binds to intracerebral glutamic acid decarboxylase (GAD) which is the enzyme responsible for the conversion of glutamate to GABA (Figs. 3 and 4).

4.1.3. Pyridoxine dependent seizures

Pyridoxine dependent seizures (PDS), a rare autosomal recessive disorder that occurs in the first few weeks of neonatal life, were first described in 1954 [4]. There is a mutation of the ALDH7A1 (antiquitin) gene leading to an accumulation of D1-piperideine-6-carboxylase enzyme [6]. This enzyme inactivates P5P, thus, preventing GABA production. Diagnosis is made by showing a clinical response to pyridoxine followed by detection of the biomarkers and/or molecular testing [6,7]. Pyridoxine dependent seizures clinically and electrographically respond to large doses of pyridoxine.

4.1.4. Pyridoxine responsive seizures

Seizures with a partial response to pyridoxine supplementation are called pyridoxine responsive seizures (PRS). PDS requires life-long supplementation whereas PRS only requires transient repletion of the pyridoxine.

An editorial published in 1998 recommended that pyridoxine be administered to patients who had seizures that have failed to improve with benzodiazepines. Dosing is not weight based. Pyridoxine can be given in 100 mg boluses, repeated every 10 min up to five doses or until a response is seen [6,8]. Normalization of the EEG should be seen within minutes of administration [4].

4.1.5. GABA and its role in seizure control

Without P5P, GABA cannot be synthesized, and glutamate remains elevated in the synapse, thereby, increasing neuronal excitability. Gamma-aminobutyric acid deficiency is seen in pyridoxine dependent genetic epilepsy. A number of factors can lower pyridoxine levels including malabsorption, inflammation, kidney disease, alcohol dependence, pregnancy, obesity, and antiepileptics (valproic acid, phenytoin, carbamazepine).

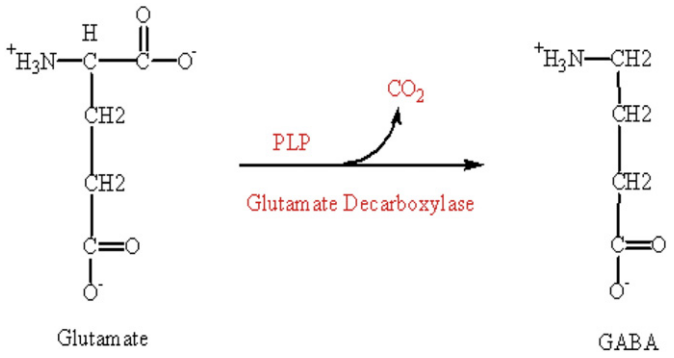

Fig. 3. Conversion of glutamate to GABA.