Pyridoxine Deficiency in Children Treated with Isoniazid

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Isoniazid-induced deficiency of pyridoxine (vitamin B₆) is reportedly not uncommon in adults but rare in children. In the present study, 38 children had serum levels of pyridoxine tested while receiving therapy with isoniazid. A biologic assay using the protozoan *Tetrahymena thermophila* determined pyridoxine status after 2 to 18 months of therapy with isoniazid. Five children (13 percent) were deficient. None had definitive clinical symptoms or signs consistent with pyridoxine deficiency. Three had normal nerve conduction velocity. Children receiving isoniazid in dosages greater than 10 mg/kg/day had a higher incidence of deficiency. Present recommendations for withholding pyridoxine prophylaxis from children receiving isoniazid therapy must be reconsidered in light of these findings, particularly in those children who are debilitated or have a poor nutritional history with a known pyridoxine deficit prior to therapy with isoniazid.

Pyridoxine (vitamin B₆) deficiency occurs in about 2 percent of those adults receiving therapy with isoniazid in dosages of 3 to 5 mg/kg/day and in 10 percent or more of those receiving higher dosages.¹² Adults at high risk are frequently given routine prophylaxis with pyridoxine to prevent this complication.³⁴ Reports of preadolescent clinical deficiency syndrome in the United States are rare and are limited primarily to those children who are malnourished,¹ those receiving high dosages of isoniazid (greater than 25 mg/kg/day) and following ingestion of large amounts of isoniazid.⁵⁷ Morales and Lincoln,⁹ in a study of 20 children, concluded that pyridoxine deficiency does not result from therapeutic doses of isoniazid. Although there is no known reason that young children should be spared this toxic effect, supplemental pyridoxine is not recommended for prepubertal children who receive therapy with isoniazid.³⁵⁹

Following the occurrence of an afebrile seizure in a four-year-old girl receiving therapy with isoniazid, 37 children below the age of 12 years who were receiving isoniazid for tuberculosis were studied for pyridoxine deficiency.

**Materials and Methods**

The child with seizures and 37 other patients were randomly selected from the Child Chest Clinic and those hospitalized for tuberculosis at the Medical College of Virginia. The clinical characteristics of the 38 children are summarized in the following table (numbers represent number of children, unless otherwise stated):

<table>
<thead>
<tr>
<th>Age</th>
<th>6.4 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>11 mo-11 yr</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>17/21</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Tuberculosis: current disease, 38</td>
</tr>
<tr>
<td>Therapy</td>
<td>Isoniazid, 38</td>
</tr>
<tr>
<td>Mean dosage, mg/kg</td>
<td>10.8</td>
</tr>
<tr>
<td>≤10 mg/kg</td>
<td>12</td>
</tr>
<tr>
<td>&gt;10≤15 mg/kg</td>
<td>23</td>
</tr>
<tr>
<td>&gt;15 mg/kg</td>
<td>3</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>5</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>5</td>
</tr>
<tr>
<td>Rifampin</td>
<td>2</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>2</td>
</tr>
<tr>
<td>Multivitamins</td>
<td>11</td>
</tr>
<tr>
<td>Serum pyridoxine levels</td>
<td>45.8</td>
</tr>
<tr>
<td>Mean level, ng/ml</td>
<td>&lt;25 ng/ml</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

No patient with a known preexisting neurologic disorder was included in the studied group, with the exception of one patient who had suffered an impact seizure seven years earlier but was otherwise normal. Dietary history and vitamin intake history were also noted, but the protein content of the diet was not calculated.

In addition to the initial history and physical examination, further history was directed toward the identification of neurologic symptoms. Serum pyridoxine levels were determined after 2 to 18 months of isoniazid therapy by pyridoxine assay using *Tetrahymena thermophila*, normal serum pyridoxine levels determined by 95 percent confidence limits are 29 to 83 ng/ml (mean, 38 ng/ml).³⁰ Complete blood cell count with differential cell count and levels of serum electrolytes, blood urea nitrogen, glucose, calcium, phosphorus, serum glutamic-oxaloacetic transaminase, lactic dehydrogenase, alkaline phosphatase, and albumin were also monitored. Repeat determinations were performed on five patients with abnormal or borderline pyridoxine serum levels. Blood was randomly drawn in the early afternoon following clinical evaluation. In addition, three patients with abnormal pyridoxine serum determinations received nerve conduction studies and electromyography.

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RESULTS

Five patients (13 percent) had pyridoxine serum deficiency with levels below 25 ng/ml (Table 1). Primary pulmonary tuberculosis (III tuberculosis with disease, lymphatic) was present in four of the pyridoxine-deficient patients, and the other had pulmonary tuberculosis (III tuberculosis with disease, pulmonary). Only one with deficiency received isoniazid at a dosage of less than 10 mg/kg/day; one also received p-aminosalicylic acid. The total number of patients receiving isoniazid at 10 mg/kg/day was 26, and five received additional antituberculosis therapy. The length of isoniazid therapy when serum pyridoxine was determined ranged from two to ten months in deficient children and from 2 to 18 months in normal children. Two of the four patients with abnormal pyridoxine serum levels and nine with normal pyridoxine determinations received multivitamins. Compliance with vitamin therapy is unknown. Dietary histories were reviewed and indicated that all except patient 5 (Table 1) received adequate nutrition. The early dietary history of this patient is suspect when she was initially pyridoxine-deficient. This patient showed pyridoxine levels of 22, 33, and 121 ng/ml at 3, 6, and 12 months of therapy; the latter two were after removal from her natural home and general improvement of many factors, no doubt including change of diet.

Developmental lag and hyperactivity were reported in patient 5. Following completion of the course of isoniazid, the patient was reported as less hyperactive, but developmental delay continued without another cause being identified. Two other children with a normal pyridoxine serum level were also said to have nonspecific changes in behavior while receiving isoniazid. In the first child we studied after a convulsion, the serum level of pyridoxine was normal, and that convulsion proved to be the first indication of later epilepsy characterized by both complex partial and secondary generalized tonic/clonic seizures. History and physical examination yielded no evidence of peripheral neuropathy, dermatologic abnormality, or other neurologic symptoms besides altered behavior as described previously. The index case and patients 2, 3, and 5 (Table 1) had nerve conduction studies and electromyograms, which were normal.

DISCUSSION

Vitamin B₆ may occur naturally in one of three forms: as pyridoxine, pyridoxal, and pyridoxamine. Pyridoxal phosphate and pyridoxamine phosphate are the physiologically active forms. As pyridoxal phosphate, vitamin B₆ is a coenzyme for a variety of metabolic transformations.

Spies and associates described the adult pyridoxine-deficient state as a syndrome of weakness, irritability, nervousness, insomnia, and difficulty in ambulation. Coursin, as previously noted by Snyderman et al in 1953, reported seizures and irritability in infants fed pyridoxine-deficient formula. Isoniazid-induced deficiency of pyridoxine was described in 1954 by Biehl and Vilter, who noted a peripheral neuropathy in adults. This syndrome is dose-related, and susceptibility is greatest in those with slowed metabolism of isoniazid secondary to hepatic disease or hereditary slow inactivation.

In patients receiving isoniazid at a dosage of 3 to 5 mg/kg/day, clinical deficiency has been reported in 2 percent of the cases, and approximately six months are required for clinical manifestations to occur. With higher dosage (isoniazid, 6 mg/kg/day), symptoms often appear within three to five weeks and may be present in more than 10 percent of the patients, directly dependent upon total daily dose and length of treatment. These discoveries have led to recommendations for routine pyridoxine prophylaxis in only some who receive isoniazid. The recommended daily minimum requirement for pyridoxine is age-dependent, ranging from 0.3 to 2.7 mg/day and is increased by higher protein intake and certain clinical states such as pregnancy. Although uncommon, primary pyridox-
Pyridoxine deficiency may still occur because of inadequate general nutrition. Volunteers with pyridoxine deficiency induced by antagonist 4-deoxypyridoxine have presented with a variety of symptoms including loss of weight, increased susceptibility to infection, mild antibody deficiency, hyperalaxuria, hypochromic anemia, and dermatologic and neurologic abnormalities, including electroencephalographic changes. The mechanism of isoniazid-induced pyridoxine deficiency is not completely understood. Biehl and Vilter postulated the formation of an isonicotinyl-pyridoxal Schiff base which is cleared by the kidney, thereby depleting the body stores of pyridoxine. Others have concluded that the increase in urinary excretion of pyridoxine is not sufficient to account for the depletion of body stores and point out that there is clinical evidence of pyridoxine deficiency without evidence of increased excretion of body stores of pyridoxine.

Additional factors associated with pyridoxine deficiency in man include chronic hepatic disease, neoplasia, uremia, alcoholism, pregnancy, and the administration of oral contraceptive steroids, penicillin, cycloserine, and hydralazine. None of our study patients had these illnesses nor received these medications.

That isoniazid-induced deficiency of pyridoxine is rare in prepubertal children unless associated with ingestion of toxic doses is a conclusion primarily based upon the results of a study by Morales and Lincoln, in which 20 children aged 2 to 13 years received isoniazid for various periods. There was neither clinical nor biochemical evidence of pyridoxine deficiency. The test used for proving deficiency was a urinary test for conversion of tryptophan to N-methyl nicotinamide. While one 12-year-old girl failed to exhibit a significant increase in urinary excretion of methyl nicotinamide in response to tryptophan load, the case was not considered significant because of her age. Therefore, it was concluded that prophylaxis was unnecessary in children receiving therapy with isoniazid. Since then, at least two reports using the same method have shown some subclinical pyridoxine deficiency in children receiving isoniazid.

Although previous studies have used the tryptophan test and relied upon excretion of xanthurenic acid, a test not correlated with clinical pyridoxine deficiency, it was elected in this study to use a microbiologic assay. This is a superior method because the organism T. thermophila has a mammalian-like requirement for pyridoxine and permits direct measurement of all metabolically active vitamin B6 in man. The older method, the primary determination of an individual enzyme, may not give a true reflection of the total level of vitamin B6. Furthermore, urinary tests frequently produce both false-positive and false-negative results. Increased excretion of xanthurenic acid has been documented in patients with elevated l-tryptophan levels and those taking certain medications or suffering from a variety of diseases.

In the present study the biologic assay demonstrated that five patients had deficient pyridoxine levels of <25 ng/ml. An additional four patients had levels between 25 and 30 ng/ml, and one question whether these patients would have developed abnormalities if longer periods of treatment were used. It is important that four of the five deficient children were given dosages of isoniazid in excess of 10 mg/kg/day. Only one received an additional antituberculosis drug, p-aminosalicylic acid. From our small sample, it does not seem that length of therapy is important, but this will require further investigation.

An important question arises from these findings. Why were these children with deficient pyridoxine levels not symptomatic? As stated previously, initial studies showed that symptoms appeared in adults after three to five weeks of therapy. One might postulate that our patients' serum levels represent early subclinical pyridoxine deficit, with adequate tissue levels still preserved because of general nutritional status, thus allowing the children to be asymptomatic. When tissue levels become depleted, symptoms of deficiency appear. Hence, serum pyridoxine depletion represents the earliest sign of impending clinical deficit. The literature further suggests that debilitated adult patients are more likely to show clinical signs of pyridoxine deficiency. A recent study surveying the vitamin B6 status of 35 preschool children estimated that 17 percent of the children had pyridoxine intake less than two-thirds of the recommended daily requirement, and 9 percent had inadequate vitamin B6 status as indicated by serum pyridoxal phosphate levels below 8.5 ng/ml; none were symptomatic for deficiency.

The results of our study suggest that recommendations for pyridoxine prophylaxis during isoniazid therapy for children should be reexamined. When the serum pyridoxine level indicates a risk of pyridoxine deficiency, the children should receive pyridoxine with the isoniazid therapy. Urinary testing for pyridoxine deficiency should be replaced with more accurate methods such as the bioassay used in this study. Although children with lowered pyridoxine levels in this study were apparently asymptomatic, tests of fine-motor coordination, learning skills, and other cognitive and behavioral modalities were not carried out. A large cooperative study will be necessary in order to answer the question of exactly which children need concomitant pyridoxine supplementation while receiving isoniazid. Although not included in our group, adolescents should also be studied to see if there is truly an unfavorable influence on pyridoxine metabolism from several factors including self-restrictive diets, metabolic factors associated with endocrine function, use of contraceptive drugs, and occasional...
unsuspected pregnancies. The pretreatment pyridoxine status should be documented, and adolescents need to be included in the studied group. Until then, we recommend pyridoxine prophylaxis for those children receiving isoniazid therapy who have a demonstrated pyridoxine deficit and those who are suspect for deficiency because of malnourishment, other disease that would predispose them to pyridoxine deficiency, and those receiving high dosages of isoniazid.

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