The New England
Journal of Medicine



Volume 309 AUGUST 25, 1983 Number 8

# SENSORY NEUROPATHY FROM PYRIDOXINE ABUSE

## A New Megavitamin Syndrome

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**Abstract** We describe seven adults who had ataxia and severe sensory-nervous-system dysfunction after daily high-level pyridoxine (vitamin $B_6$) consumption. Four were severely disabled; all improved after withdrawal. Weakness was not a feature of this condition, and the central nervous system was clinically spared. Although consumption of large doses of pyridoxine has gained wide public acceptance, this report indicates that it can cause sensory neuropathy or neuronopathy syndromes and that safe guidelines should be established for the use of this widely abused vitamin. (N Engl J Med 1983; 309:445-8.)

PYRIDOXINE, an essential, water-soluble vitamin ($B_6$), is a coenzyme for many decarboxylation and transamination reactions; the minimum daily requirement for normal adults is 2 to 4 mg. It is generally held that "the water-soluble vitamins are among the safest substances known,"[1] and that vitamin $B_6$ is not associated with human neurotoxicity. Tablets containing 50 to 500 mg of pyridoxine are widely available. Pyridoxine has gained public acceptance as a component of body-building regimens and as a remedy for the premenstrual syndrome[2] and has been claimed to be medically effective in treating the carpal-tunnel syndrome.[3] Extremely high doses (600 to 3000 mg per day) have been administered to schizophrenics[4] and autistic children,[5] without reported side effects, and doses up to 2 g per day have recently been suggested for the treatment of childhood hyperkinesis.[6] The present report demonstrates that serious neurotoxicity may be associated with pyridoxine megavitaminosis.

## CASE REPORTS

The dosage schedule of each case is shown in Table 1.* The typical clinical presentation was exemplified by the following case.

### Case 6

A 27-year-old woman sought medical attention because of increased difficulty in walking. Approximately two years previously she had been told that vitamin $B_6$ provided a natural way to get rid of body water, and she had begun to take 500 mg per day for premenstrual edema. One year before presentation, she had started to increase her intake, until she reached a daily intake of 5 g per day. During this period of increase in dosage, she initially noticed that flexing her neck produced a tingling sensation down the neck and into the legs and soles of her feet (Lhermitte's sign). In the four months before neurologic evaluation, she became progressively unsteady when walking, particularly in the dark, and noticed difficulty handling small objects. She also noticed some change in the feeling in her lips and tongue, but she had no other positive sensory symptoms and was not aware of any limb weakness.

Examination showed that the patient could walk only with the assistance of a cane. Her gait was broad-based and stamping, and she was unable to walk at all with her eyes closed. She had marked pseudoathetosis of the outstretched arms. Her muscle strength was normal. All limb reflexes were absent. Babinski signs were not present. The sensations of touch, temperature, pinprick, vibration, and joint position were severely impaired in both the upper and lower limbs. There was a mild subjective alteration of touch-pressure and pinprick sensation over the cheeks and lips but not over the forehead. As in the other cases, the results of spinal-fluid examination were normal, as were those of all other clinical laboratory investigations. Electrophysiologic studies included determina-

*See NAPS document no. 04116 for two pages of supplementary material (more clinical features of each case). Order from NAPS c/o Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance (in U.S. funds only) $7.75 for photocopies or $4 for microfiche. Outside the U.S. and Canada add postage of $4.50 ($1.50 for microfiche postage).

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Supported by grants (OH-00535, OH-00851, and NS-08075) from the U.S. Public Health Service.

Table 1. Features of Seven Cases of Pyridoxine Abuse.

| Case No. | Age/Sex | Reason for Taking $B_6$ | Maximum Daily Dose | Duration of Consumption |
|---|---|---|---|---|
| 1 | 36/F | Health magazine advocated it for menstrual edema | 2 g | 4 mo |
| 2 | 25/M | Self-imposed dietary supplement | 3 g | 4 mo |
| 3 | 35/F | Self-imposed dietary supplement | 2 g | 40 mo |
| 4 | 34/F | Gynecologist prescribed it for edema | 2 g | 34 mo |
| 5 | 20/M | Orthomolecular psychiatrist prescribed it | 6 g | 3 mo |
| 6 | 27/F | Self-imposed treatment for edema | 5 g | 2 mo |
| 7 | 43/F | Gynecologist prescribed it for edema | 4 g | 10 mo |

tions of motor-nerve and sensory-nerve conduction in the arms and legs, needle electromyography, and the somatosensory evoked response from tibial and median nerves. No sensory-nerve action potentials could be elicited, and motor-nerve conduction and an electromyogram were normal. In somatosensory evoked-response studies, unilateral tibial-nerve stimulation produced no response; bilateral tibial-nerve stimulation produced no responses over the lumbar or cervical spine, but a cerebral response of very low amplitude was noted. Median-nerve stimulation produced a low-amplitude response at the brachial plexus but not at more proximal sites.

Approximately two months after withdrawal from pyridoxine, the patient reported the beginning of improvement in gait and sensation. Seven months after withdrawal, she felt much improved; she could walk steadily without a cane, could stand with her eyes closed, and had returned to work. Occasional "lightning-like" pains occurred in the calves and shins, especially after exercise. Neurologic examination disclosed that her strength was still normal and that tendon reflexes remained absent throughout. Her feet still had a severe loss of vibration sensation but definite improvement in the sense of joint position, touch, temperature, and pinprick. In the upper limbs there was only a mild impairment of vibration sensation; the joint-position sense was normal. Electrophysiologic studies revealed that sensory-nerve responses were still absent but motor-nerve conduction remained normal. Studies of somatosensory evoked response showed definite improvement in central conduction; bilateral tibial-nerve stimulation produced a normal-amplitude response at the scalp, although there was no response over the spine. Median-nerve stimulation produced essentially normal responses over the brachial plexus, cervical spine, and cerebrum. There was a slight delay between the clavicular and cervical-spine responses (N9 to N13 delay).

In summary, after seven months of abstinence from pyridoxine, the patient had great improvement in symptoms, moderate improvement in signs, no improvement in peripheral sensory conduction, and a marked recovery of central conduction.

### Other Cases

The clinical profile was similar in all cases. Unstable gait and numb feet usually heralded the illness. Most of the women changed to low-heeled shoes and remained employed, with a restricted range of walking, until they were unable to go to work. Numbness and clumsiness of the hands followed within months and impaired their typing skills. Perioral numbness, when present, was the last symptom to appear. All patients had a "stocking–glove" distribution of sensory loss, with strength strikingly preserved. The sensory profile in severely affected patients was nearly total loss of appreciation of all modalities; less affected patients consistently had relative sparing of the senses of pinprick and temperature. Lumbar puncture was performed in Cases 2, 5, and 6; the cerebrospinal fluid was unremarkable in each. Sural-nerve biopsy, performed in Cases 3 and 4, revealed widespread, nonspecific axonal degeneration affecting large and small myelinated fibers (Fig. 1). Distal sensory-nerve conduction was absent in all nerves except in Cases 2 and 7, whose median nerves had moderate slowing. Motor-nerve conduction was normal throughout in every case, except for slight slowing in peroneal nerves of Cases 4 and 5. Upper-limb and lower-limb somatosensory evoked responses in Cases 5 and 6 indicated severe impairment of proximal tibial-nerve conduction in both patients and moderately impaired proximal median-nerve conduction in Case 6. Proximal median-nerve conduction was normal (60 m per second) in Case 5. Each patient underwent an extensive clinical and laboratory evaluation to rule out additional toxic, metabolic, or immunologic factors. None had a family history of neuropathy except for Case 2, whose older, chronically schizophrenic brother had committed suicide during the development of a similar sensory neuropathy from megavitamin pyridoxine therapy.

The maximum daily consumption of pyridoxine ranged from 2 to 6 g; however, only Cases 2 and 5 began taking the vitamin at such high doses. The other patients began with 50 to 100 mg per day and steadily increased their intake in an attempt to achieve a therapeutic level; none experienced symptoms at doses below 2 g per day. In Case 7 the plasma pyridoxine level was in excess of 30 ng per milliliter (normal, 3.6 to 18) at the initial examination. She had taken her usual daily 4-g dose three hours earlier. Her plasma pyridoxine level fell to 17 ng per milliliter after one month's abstinence. Pyridoxine was the sole nutritional supplement in six cases; one patient (Case 3) also took a multivitamin preparation and a liquid-protein

solution. In no instance did pyridoxine have an appreciable effect on edema, sense of well-being, or an underlying psychiatric condition. Substantial improvement occurred in all cases in the months after withdrawal from pyridoxine; usually, improvement in gait and less discomfort in the extremities were noted within two months. The four patients followed for at least six months after withdrawal of pyridoxine felt dramatically improved by then, although careful neurologic examination usually disclosed diminished distal sensory perception at this stage. Vibratory sense was usually most severely affected, and patients recovered less of it than other modalities. Cases 1 and 3, followed for three and two years, respectively, have almost completely recovered.

## Discussion

We have described seven adult patients in whom gradually progressive sensory ataxia and profound distal limb impairment of position and vibration sense developed after consumption of large doses of pyridoxine. The senses of touch, temperature, and pain were less affected, and except for minimal involvement of toe extensors, weakness was not a feature of this illness. All tendon reflexes were diminished or absent, and no signs of central-nervous-system dysfunction were apparent, except for a transient Lhermitte's sign in three cases. Studies of nerve conduction and somatosensory evoked responses indicated dysfunction of distal portions of sensory peripheral nerve, and nerve biopsies in two patients demonstrated widespread, nonspecific axonal degeneration. Neurologic disability gradually improved once the patients stopped taking pyridoxine, and those examined after a prolonged follow-up period had made a satisfactory recovery. Overall, this constellation of findings is most compatible with a toxic, primarily sensory neuropathy of the distal axonopathy or neuronopathy type.[7,8]

Clinical evaluation of these seven patients implicates pyridoxine megavitaminosis as the sole cause of their illness. This conclusion is further strengthened by studies in which rats and dogs receiving high doses of pyridoxine hydrochloride (200 mg to 1 g per kilogram of body weight) acquired a progressively unsteady gait.[9-12] Histopathological examination of the nervous system in three studies of dogs revealed selective degeneration of the sensory neurons of the dorsal root and gasserian ganglia and their central and peripheral processes (sensory neuronopathy).[9,11,12] Another study, which used lower doses, showed nerve-fiber degeneration, which was most severe in distal portions of sensory axons of these same cells (sensory distal axonopathy), with relative sparing of the cell body.[13-15] Taken in concert, all these studies indicate that the mammalian peripheral sensory nervous system is vulnerable to sustained megavitamin doses of pyridoxine, and they provide a clinicopathological foundation for the disease encountered in our seven patients.

The pathogenesis and biochemical basis of pyridoxine neurotoxicity are unknown. It has been suggested that toxic peripheral sensory neuronopathy syndromes reflect a particular vulnerability of the neurons of the dorsal-root ganglia to circulating toxins, because of the permeability (i.e., the absence of a blood–brain barrier) of their associated blood vessels.[16] The purely sensory syndrome produced by megadose pyridoxine may also reflect the anatomic vulnerability of these cells, since vitamin $B_6$ is transported into the central nervous system by means of a saturable mechanism and since other central-nervous-system neurons may be relatively shielded from excessive levels of circulating pyridoxine.[17]

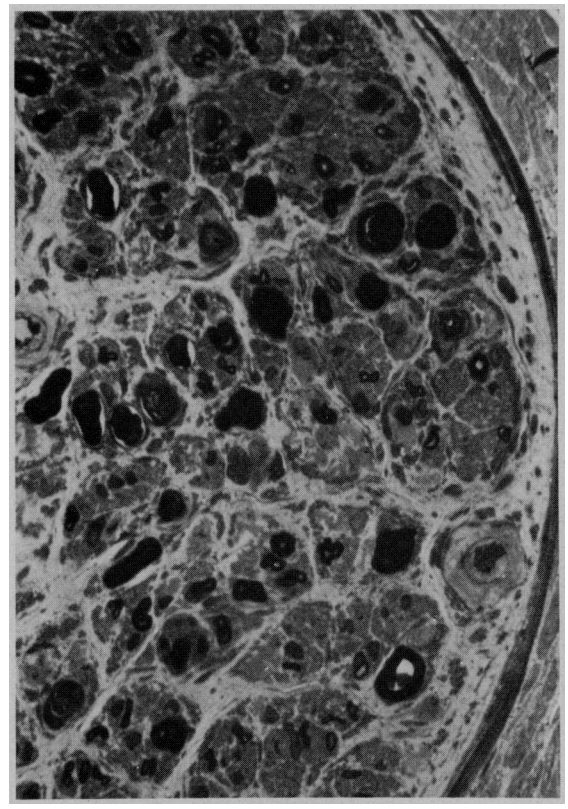

Figure 1. Cross Section of Sural Nerve from Case 3, Obtained after Nine Months of Pyridoxine Abuse (2 g per Day).
There is severe fiber loss, and some myelinated fibers are undergoing degeneration (×720).

Since pyridoxine is used to treat peripheral neuropathy associated with isoniazid or hydralazine therapy, the idea that it can cause neuropathy seems at first improbable or paradoxical. This medical use of pyridoxine — an essential vitamin — as an antineurotoxic agent, combined with a widely held, scientifically unsupported belief that it has anti-edema properties, has contributed to its acceptance as a generally safe substance. General acceptance was an important factor in four of our cases, who began self-imposed therapy at innocuous levels and gradually increased the dose on the assumption that vitamin $B_6$ was safe and that "more might be better." It is clear that long-term megavitamin pyridoxine therapy is not safe.

Limits should be put on its use, and safe levels established through further experiments in animals or in vitro. Megavitamin therapy with vitamin $B_6$ for behavioral disorders should be strongly discouraged, as has recently been done with vitamin A use, until the value of such treatment has been clearly determined through controlled studies and safe guidelines for pyridoxine therapy have been established.[18]

We are indebted to Ms. Patricia Vacchelli for helping to prepare the manuscript and to Dr. Jasper Daube (Mayo Clinic) for allowing us to present the electrophysiologic studies of Case 6.

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# HOMOCYSTINURIA — THE EFFECTS OF BETAINE IN THE TREATMENT OF PATIENTS NOT RESPONSIVE TO PYRIDOXINE

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**Abstract** The treatment of homocystinuria that is not responsive to pyridoxine is not usually biochemically or clinically successful, and vascular, ocular, and skeletal complications commonly supervene. Persistent marked homocysteinemia appears to be the most important biochemical disturbance leading to these complications. Ten patients with cystathionine $\beta$-synthase deficiency that was not responsive to pyridoxine and one patient with homocystinuria due to a defect in cobalamin metabolism were treated with 6 g daily of betaine added to conventional therapy, to improve homocysteine remethylation. All patients had a substantial decrease in plasma total homocysteine levels ($P<0.001$) and an increase in total cysteine levels ($P<0.001$). Changes in plasma methionine concentrations were variable. Fasting levels of plasma amino acids became normal in two patients, and in six there was immediate clinical improvement. There were no unwanted effects. We conclude that treatment of homocystinuria that is not responsive to pyridoxine and of disorders of homocysteine remethylation should include betaine in adequate doses to ensure maximum lowering of elevated plasma homocysteine levels. (N Engl J Med 1983; 309: 448-53.)

THE inborn errors of methionine metabolism that result in homocystinuria are of special interest, because, like homozygous familial hyperlipoproteinemia, they provide a model for premature atherogenesis in human beings. Homocystinuria has an incidence of approximately 1 in 60,000 in New South Wales, Australia[1] (although lower incidences have been reported elsewhere[2]), and is usually due to diminished activity of cystathionine $\beta$-synthase (EC 4.2.1.22), which condenses homocysteine and serine to form cystathionine (Fig. 1 and 2). As a consequence, plasma concentrations of homocysteine, cysteine–homocysteine, and methionine are elevated, and the level of cysteine is decreased. In addition to thromboembolism and early atherosclerosis — which are the usual causes of premature death — dislocated lenses, skeletal deformity, and mental retardation are common features of the disease.[2] In the other, rarer forms of homocystinuria due to defects affecting the folate remethylating pathway (Fig. 1), in which the level of plasma homocysteine is elevated, but the level of plasma methionine is normal or depressed, premature atherosclerosis is also found.[3,4]

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