Abnormally High Pyridoxine Requirement

SUMMARY OF EVIDENCE SUGGESTING RELATION BETWEEN THIS FINDING AND CLINICAL PYRIDOXINE "DEFICIENCY"

By ANDREW D. HUNT, JR., M.D.*

THE EVIDENCE for the existence of a congenitally abnormally high requirement for vitamin B_6 has been slowly accumulating since the first demonstration by Snyderman *et al.*[1] of the effects of deficiency of this vitamin in the human infant.

Beginning in 1951, an outbreak of convulsions in infants, usually less than four months of age, was observed in widely scattered parts of the United States and reported by several authors.[2-5] It was ascertained that the common denominator in these cases was the diet; namely a brand of liquid, infant-feeding mixture which, due to changes in autoclaving procedures, was found to contain in the neighborhood of 60 mcg of vitamin B_6 per reconstituted quart. The syndrome was remarkably uniform, with irritability, "colic," and general unhappiness being followed by severe, often prolonged generalized convulsions. Changing to another formula, or giving vitamin B_6 by mouth or parenterally, promptly stopped the seizures.

Routine study of these infants, in general, revealed essentially normal findings, with the exception of somewhat elevated spinal fluid protein in some cases. The electroencephalogram was normal except during a seizure, and this seizure pattern was shown[4] to revert to normal with remarkable rapidity upon the intramuscular administration of a large dose of pyridoxine.

From the Hunterdon Medical Center, Flemington, New Jersey, and the Department of Pediatrics, New York University College of Medicine.

* Director of Pediatric Services, Hunterdon Medical Center, Flemington, New Jersey, Assistant Professor of Pediatrics, New York University College of Medicine, New York, N. Y.

However, the actual number of infants developing convulsions was a very small percentage of those who were fed the deficient feeding mixture.

This problem has recently been studied by Bessey *et al.*[2,3] who investigated five such infants. One liter per day of an evaporated milk mixture, containing an estimated 0.25 mg of vitamin B_6 was sufficient to prevent further seizures. In one of these infants, intensive biochemical studies were performed, and 1.0 to 1.2 mg of vitamin B_6 was required to prevent xanthurenic acid excretion after a tryptophane load. It seems unfortunate that these authors did not have the opportunity for a similar study of the other infants who convulsed on the pyridoxine-poor mixture, for the findings in this one case suggest an explanation for selection of susceptibility to a nearly adequate intake of vitamin B_6. In the control group of eight infants, xanthurenic acid excretion after a tryptophan load was prevented in all but one case by amounts of pyridoxine ranging from 0.2 to 0.4 mg. In this one exceptional case, considerable xanthurenic acid was excreted in spite of a pyridoxine intake of 0.20 mg. Titration of intake necessary to prevent this finding was not performed, but excretion of xanthurenic acid was eliminated by a single dose of 5 mg of pyridoxine hydrochloride. The authors, however, assume that this baby's vitamin B_6 requirement to prevent xanthurenic acid excretion was above 1 mg daily, as was the case in the convulsing infant who was so tested.

Thus, any statistical difference between the control and experimental groups is lacking, and one can only speculate that the control infant with the apparently high vitamin B_6 re-

quirement would have convulsed if given the pyridoxine-poor feeding, and that a suggestion exists that the infants who suffered convulsions on the deficient commercial milk preparation were actually subjects with a pyridoxine requirement which is higher than usual.

Bessey *et al.* also describe two breast-fed infants with convulsions relieved by a calculated intake of 0.26 mg pyridoxine daily. These two infants also required upwards of 1.0 mg pyridoxine to prevent excretion of xanthurenic acid after a tryptophan load. The breast milk given one of these infants was found to contain but 0.067 mg per quart of pyridoxine.

Thus, the suggestion is again apparent that convulsions may occur in susceptible infants as a result of a borderline intake of vitamin B_6, and that such a barely adequate intake can occasionally at least be a natural phenomenon. It is emphasized by the authors that the amount of vitamin B_6 required to prevent excretion of xanthurenic acid after a tryptophan load is markedly greater than that required to prevent convulsions. It is assumed that two different vitamin B_6 dependent mechanisms are being reflected in the two end points. Thus it is thought that the biochemical evidence for vitamin B_6 deficiency is more sensitive than the clinical manifestation and will appear first in the course of progressive withdrawal of the vitamin. Conversely, with clinical symptoms of pyridoxine deficiency, these manifestations are abolished with a smaller amount of vitamin B_6 than is the excretion of xanthurenic acid after a tryptophan load.

First reported in 1952, and published in 1954[6] was the case of a newborn female infant suffering from intractable convulsions which failed to respond to the usual anticonvulsant measures. All studies were essentially unrevealing except for a markedly increased spinal fluid protein. Eventually, and quite by accident, it was discovered that the intramuscular injection of a multivitamin preparation containing 6 mg pyridoxine abruptly brought an end to the convulsions, and that the duration of effect was slightly upward of 48 hours. Finally, 2 mg of pyridoxine given orally was found to prevent convulsions for approximately 48 hours, and nearly two years later this dose was still apparently necessary to maintain the child in a seizure-free state.

Xanthurenic acid was not excreted after a tryptophan load in this case. It was concluded that this infant did not represent the characteristic picture of vitamin B_6 deficiency, but rather that she was suffering from a metabolic aberration producing an abnormal need for pyridoxine, either as a result of increased destruction of the vitamin, or of some other mechanism. Of interest was the fact that the child's mother had received large amounts of intramuscular vitamin B_6 during the first trimester of pregnancy, because of severe nausea and vomiting. She had had two previous pregnancies. The first, during which there had been no pyridoxine medication, had resulted in the birth of a normal infant. During the second pregnancy, vitamin B_6 had been given during the first three months, and the baby had died in the neonatal period with severe convulsions. It was therefore tempting to relate the pyridoxine "dependency" to the vitamin B_6 medication during pregnancy.

An attempt was made to subject this hypothesis to an experimental test. It is known that suckling rats, with their mothers on a pyridoxine-deficient diet, lose weight, frequently convulse at about three weeks of age, and some die. Pregnant rats were divided into two groups; the experimental group was given massive amounts of pyridoxine mixed in the daily ration during the first half of pregnancy; the control group was given the usual diet. After delivery, both groups were given a diet devoid of vitamin B_6. Had the theory that "dependency" was the result of vitamin B_6 administration during pregnancy been valid, one would have expected a more rapid incidence of convulsions and weight loss in the infant rats born of the mothers who had been fed loading doses of pyridoxine during pregnancy. No such correlation, however, was observed in any of the trials; indeed, if there were any positive results, they were in the opposite direction, with the offspring of the experimental group having a slightly better weight gain than those in the control group.[7] Experimental evidence in support of the hypothesis that abnormal need

for vitamin B_6 could be related to overdose of this substance during pregnancy is therefore lacking.

Bessey *et al.*[3] describe two newborn infants who appear to resemble Hunt's case.[6] They required 5 and 2 mg of vitamin B_6, respectively, to control convulsions, and both needed in the neighborhood of 2 mg per day to prevent convulsions over a period of several months. One of these infants is stated to be developmentally retarded. Neither is reported to have abnormal spinal fluid findings. One of these cases excreted no xanthurenic acid after a tryptophan load; the other excreted a small amount, which was abolished by but 0.4 mg of pyridoxine. This amount is in sharp contrast to the 5 mg required to prevent convulsions. The authors point out that these two infants, presumably representing aberrations of vitamin B_6 metabolism, demonstrate a situation quite the reverse of that seen in the infants whose convulsions were related to a decreased intake of vitamin B_6. In the latter group, it will be remembered, the quantity of pyridoxine required to prevent convulsions was much less than that required to abolish the xanthurenic acid test.

Neither of Bessey's two cases of "pyridoxine dependency" gave a history of maternal medication with vitamin B_6 during pregnancy.

Although anemia was the chief manifestation of one of Snyderman's infants[1] with induced B_6 deficiency, this does not appear to have been a significant part of the clinical picture of the thus far reported infants with symptoms related to vitamin B_6 intake. A recent report by Harris *et al.*[8] describes a case of "pyridoxine responsive anemia" in a 27-year-old man, who was first seen in 1947 with a hypochromic anemia (4.5 g hemoglobin per 100 ml) which was unresponsive to iron, liver extract, yeast, folic acid, and ascorbic acid. One year later, a spontaneous remission ensued which continued until 1953. When severe anemia recurred, pyridoxine hydrochloride, in a dosage of 200 mg intramuscularly daily for five days was accompanied by a reticulocyte response to 50.8 per cent, with a subsequent rise in hemoglobin to 13 g per 100 ml. Within 11 weeks, the hemoglobin had again fallen to 7.8 g per 100 ml. At that point, 1 mg pyridoxine intramuscularly failed to produce a response; however, 10 mg daily for seven days produced a good reticulocyte response and a rapid rise of hemoglobin to 14.1 g per 100 ml. Biochemical investigation of this patient revealed abnormalities of tryptophan metabolism which were partly corrected by 1 mg pyridoxine, and completely rectified by 10 mg.

In the older child and adult, there is evidence that convulsions[9,10] and abnormal electroencephalographic findings[10–13] may rarely be rectified by the administration of vitamin B_6. However, the preponderance of experience indicates that pyridoxine lacks a pharmacologic anticonvulsant action; trials of this substance in various forms of epilepsy have, in general, failed.[14] It would therefore appear probable that the therapeutic effect of administered pyridoxine represents the correction of a deficiency specifically at the level of central nervous system function. As in the case of pyridoxine "dependency" previously discussed, other symptoms and signs of Vitamin B_6 deficiency in the human as described by Vilter[15] were absent in these cases. It is notable furthermore that convulsions are not described by Vilter in adults made Vitamin B_6-deficient through the administration of desoxypyridoxine.

Therefore, the evidence concerning variations in body requirements for vitamin B_6, scattered and incomplete as it is, appears to indicate three general types of situation.

(1) The widespread incidence of seizures in infants fed a commercial milk preparation deficient in vitamin B_6 together with the data of Bessey *et al.* quoted above, appears to indicate moderate variation in pyridoxine requirements in normal infants. Such infants, when given feedings containing a quantity of vitamin B_6, apparently adequate for the majority of the infantile population, are likely to suffer convulsions. Although but a few such infants have been studied from this standpoint, the amount of added pyridoxine required to protect against seizures is small. It is also considerably less than the amount required to reverse the biochemical evidence of deficiency represented by the xanthurenic acid test. It is to be noted

that two of Bessey's cases were breast fed, so that this syndrome may not directly be related to cow's milk.

(2) Congenital abnormalities of metabolism of vitamin B_6, are characterized by severe convulsions in infants, in spite of usually adequate pyridoxine intake. Three such infants seem now to have been reported. The quantity of vitamin B_6 required to prevent seizures in these apparently rare cases is of a much higher order of magnitude than the effective dose in those infants in group 1. Furthermore, there seems to be a basic metabolic difference. In the three reported cases, xanthurenic acid tests were normal. Thus, there was no evidence of a biochemical deficiency even though relatively huge amounts of pyridoxine were required to prevent or stop convulsions. It therefore seems likely, in view of freedom from generalized clinical or biochemical evidence of pyridoxine lack, that these infants are suffering from a metabolic cerebral anomaly characterized by an abnormal need for, or utilization of, vitamin B_6 by the brain.

(3) The third group consists of the few adults who have had symptoms relieved by pyridoxine. Among them are the few patients whose seizures seem to have been relieved by vitamin B_6, and the well documented case of pyridoxine-responsive anemia mentioned above. The latter patient was demonstrated to have biochemical evidence of deficiency, with the identical dose of vitamin B_6 being required to reverse both the xanthurenic acid test and the clinical symptom of anemia. This is, of course, in contrast to the pyridoxine-dependent infants, where there was no demonstrable biochemical deficiency. Perhaps different metabolic systems are involved, and the evidence of pyridoxine deficiency as reflected in failure of hematopoiesis is more closely related to excretion of xanthurenic acid after a tryptophan load than is cerebral function as reflected in convulsions. Totally speculative in these adult patients must remain the question of time of onset of the abnormal need for vitamin B_6. The published evidence[8] in Harris' case of pyridoxine-responsive anemia suggests development of the condition during young adult life. However, both in the case of the anemia responsive to pyridoxine, and in the patients with convulsions relieved by this substance, the possibility exists of a genetically determined lesion finding its expression later in life.

Japanese investigators have described the production of severe thiamine deficiency in humans by intestinal thiaminase-secreting bacteria.[16] That "pyridoxinase"-secreting organisms might exist and therefore result in abnormally high vitamin B_6 requirement seems a possibility worthy of investigation.

Therefore, dependency on unusually high intake of vitamin B_6 is a rare but apparently well-documented phenomenon, which can make its appearance at any stage of life. Thus far the symptoms of the condition have been either convulsions or anemia, with or without biochemical evidence of pyridoxine deficiency. In general, as in the case of Vitamin B_6-deficient experimental animals, there appears to be a strong tendency for a deficiency of this vitamin to reveal itself by the production of convulsions in young infants, while adults show other manifestations. Present knowledge permits little more than a descriptive discussion of these metabolic lesions, the more exact definition of which must await extensive clinical and biochemical investigation.

REFERENCES

1. Snyderman, S. E., Holt, L E., Carretero, R., and Jacobs, K.: Pyridoxine deficiency in the human being. *Fed. Proc.* 9: 371, 1950; Pyridoxine deficiency in the human infant. J. Clin. Nutrition 1: 200, 1953.
2. Bessey, O. A., Adam, D. J., Bussey, D. R., and Hansen, A. E.: Vitamin B_6 requirements in infants. *Fed. Proc.* 13: 451, 1954.
3. Bessey, O. A., Adam, D. J., and Hansen, A. E.: Intake of vitamin B_6 and infantile convulsions; a first approximation of requirements of pyridoxine in infants. *Pediatrics* 20: 33, 1957.
4. Coursin, D. B.: Convulsive seizures in infants with pyridoxine deficient diet. *J. A. M. A.* 154: 406, 1954.
5. Molony, C. J., and Parmelee, A. H.: Convulsions in young infants as a result of pyridoxine (Vitamin B_6) deficiency. *J. A. M. A.* 154: 405, 1954.
6. Hunt, A. D., Jr., Stokes, J., Jr., McCrory, W. W., and Stroud, H. H.: Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. *Pediatrics* 13: 140, 1954.

7. HUNT, A. D., JR.: Unpublished observations.
8. HARRIS, J. W., WHITTINGTON, R. M., WEISMAN, R., JR., and HORRIGAN, D. L.: Pyridoxine responsive anemia in the human adult. *Proc. Soc. Exp. Biol. Med.* 91: 427, 1956.
9. ERNSTING, W., and FERWERDA, T. T. P.: Vitamin B_6 in therapy of epilepsy. *Nederl. tidjschr. geneesk.* 95: 3643, 1951.
10. TOWER, D. B.: Neurochemical aspects of pyridoxine metabolism and function. AM. J. CLIN. NUTRITION 4: 329, 1956.
11. GOZZANO, M., and COLOMBATI, S.: Die Virkung der B Vitamine auf das Elektrencephalogram. *Arch. Psychiat.* 183: 192, 1949.
12. GOZZANO, M., COLOMBATI, S., and SINISI, C.: Action des vitamines B sur l' E. E. G. des epileptiques. *Presse Med.* 57: 1072, 1949.
13. COURSIN, D. B.: Effects of vitamin B_6 on the central nervous activity in childhood. AM. J. CLIN. NUTRITION 4: 354, 1956.
14. FOX, J. R., and TULLIDGE, G. M.: Pyridoxine (Vitamin B_6) in epilepsy; a clinical trial. *Lancet* 2: 345, 1946.
15. VILTER, R. W., MUELLER, J. F., GLAZER, H. S., JARROLD, T., ABRAHAM, J., THOMPSON, C., and HAWKINS, V. R.: Effect of vitamin B_6 deficiency induced by desoxypyridoxine in human beings. *J. Lab. & Clin. Med.* 42: 335, 1953.
16. Bacterial Synthesis and Destruction of Thiamine. *Nutrition Reviews* 15: 65, 1957.