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THE CARPAL TUNNEL SYNDROME AS A PROBABLE PRIMARY DEFICIENCY OF VITAMIN B_6 RATHER THAN A DEFICIENCY OF A DEPENDENCY STATE

Satoshi Shizukuishi*, Satoshi Nishii*, John Ellis+ and Karl Folkers*

*Institute for Biomedical Research, The University of Texas at Austin Texas 78712, +103 W. 20th Street, Mt. Pleasant, Texas 75455

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SUMMARY

The mean basal specific activities and the mean % deficiencies of the activity of the glutamic oxaloacetic transaminase of the erythrocytes were identical (n.s.) for a group of eight patients with a severe carpal tunnel syndrome and for a group of eight university students. There was no significant difference in the increases in the specific activities for the patients and the students at 4 concentrations of pyridoxal 5'-phosphate. The apparent K_m for the patients and the students was 95 μM and 61 μM (n.s.) respectively. It is concluded from these data in conjunction with previous findings that the carpal tunnel syndrome is a deficiency disease of vitamin B_6, which is probably primary rather than one of a dependency state.

INTRODUCTION

No effective chemotherapy had been established for the idiopathic carpal tunnel syndrome, which is a widely existing disease in the population. Only orthopedic surgery has been widely practiced for relief of the neurological compression. The benefit of such surgery is erratic, and can be of limited duration Data from 1215 patients at the Mayo Clinic during 1930-60 were reviewed by Yamaguchi et al. (1). The symptoms of these patients had been recognized for up to 40 years; 85% were over 40 in age; 459 were surgically treated. The medical literature abounds with diverse reports on the entrapment syndromes which appear to exist separately and in conjunction with many other diseases, commonly, rheumatoid arthritis, obesity, etc. Morelli and Sala (2) stated that--"the treatment--clearly must be surgical" and Dolenc and Trontelj (3) stated--"microsurgery is a method of choice in the treatment of pressure neuropathies".

The status of vitamin B_6, as the coenzyme pyridoxal 5'-phosphate, was determined by the specific activities (S.A.) and the % deficiencies of activity of the glutamic oxaloacetic transaminase of the erythrocytes (EGOT) of ten patients having a severe clinical status with a primary diagnosis of the carpal tunnel syndrome. All of these patients showed a severe deficiency ($p<0.001$) of vitamin B_6 by comparison of the S.A. of EGOT with that of a control group. The deficiency was revealed by a highly standardized assay based upon the principle of unsaturation and saturation of a coenzyme-apoenzyme system, i.e., EGOT. Therapy of these ten patients with pyridoxine resulted in a great clinical improvement and anticipated surgery became unnecessary (4).

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A second group of 11 patients was also found deficient ($p<0.001$) in vitamin B_6 as established by the differential specific activities of EGOT (5). Unexpectedly, clinical improvement was difficult to evaluate ($0.01<P<0.02$) after six weeks of therapy. Then it was found that after 11 weeks, clinical improvement was unambiguous ($p<0.001$).

The unexpected timing of the biochemical and clinical responses may be explained as follows. Biochemically, oral administration of pyridoxine corrects the deficiency of pyridoxal 5'-phosphate or the unsaturation of empty receptors of the existing apoenzyme of the transaminase (EGOT) within days, but this correction was not associated with unambiguous clinical improvement. It is the correction of a deficiency in the number of molecules of the transaminase, over 10-12 weeks, which is unambiguously associated with clinical improvement. The clinical response after 10-12 weeks seems coincidental with a translational long-term increase in the number of molecules of the transaminase (EGOT) by a mechanism which appears activated by correcting a deficiency of pyridoxal 5'-phosphate.

This new knowledge on the transaminase has not only provided a biochemical diagnosis of the carpal tunnel syndrome, but has allowed the design of a successful clinical protocol for therapy, both open and double blind.

The first successful double blind trial with pyridoxine and placebo has now been reported for patients who had both the carpal tunnel syndrome and a deficiency of vitamin B_6 (6). An unbroken sequence of correct declarations without a single mistake was made for patients who had received coded pyridoxine or placebo; $P<0.00195$. Those patients on placebo were then treated with pyridoxine on a cross-over basis, and they also clinically responded to pyridoxine.

Two categories of deficiencies of vitamin B_6 and certain other vitamins are known. A primary deficiency results from an inadequate level of the vitamin in the diet. A dependency state results from a specific biochemical abnormality due to a genetic defect. Homocystinuria is a disorder of methionine metabolism, and is a known dependency state of vitamin B_6. Patients with this state have clinically responded to levels of 200-500 mg of pyridoxine daily as evidenced by a return of plasma levels of methionine and homocysteine to normal, and elimination of urinary homocystine (7).

Since 1975, the nature of the deficiency of vitamin B_6 which is associated with the carpal tunnel syndrome has been questioned toward resolving whether the carpal tunnel syndrome is a primary deficiency of vitamin B_6 or one of a dependency state. A study has been made of the nature of this deficiency as described herein.

METHODS AND MATERIALS

The enzyme methodology of Kishi *et al.* (8) was used. Blood samples of *ca.* 10 ml were drawn from the cubital vein of the subjects into "lavender" vacutainers containing 14 mg of EDTA.

RESULTS AND DISCUSSION

The EGOT data of patients with a severe carpal tunnel syndrome of university students have been compared. The mean basal S.A. of the blood samples of eight patients with the carpal tunnel syndrome was 0.24±0.04 and the mean % deficiency 38±7 (N=15). The mean basal S.A. of eight university students was 0.25±0.03 and the mean % deficiency was 37±6 (N=8).

The increases in S.A. of each blood sample from the patients and from the students were determined at 4 concentrations of pyridoxal 5'-phosphate, 33, 83, 167 and 333 mM. The data are in Fig. 1. There was no significant difference between the mean basal values of S.A. and % deficiency for the patients and the students and at any one of the 4 concentrations of pyridoxal 5'-phosphate. The data in Fig. 2 show that the apparent K_m for the patients and for the students was 95 μM and 61 μM, respectively, and there is no significant difference between these two values.

Since there is no reason to believe that these students have a dependency state of a B_6 deficiency, these biochemical data indicate that the erythrocytes of the patients also have a primary deficiency of vitamin B_6.

The clinical evidence that the afflicted tissue causing the neuropathy is also due to a primary deficiency is based upon the finding (9,10) that treatment with pyridoxine at 2 mg/day of a classical case of the carpal tunnel syndrome significantly relieved the syndrome; 2 mg/day is the known Recommended Daily Allowance. If this neuropathy were one of a dependency state, this dosage of 2 mg would not have shown such clinical response, because it is known that as much as 200-600 mg/day of pyridoxine has been necessary to produce clinical responses in B_6-dependent patients (11).

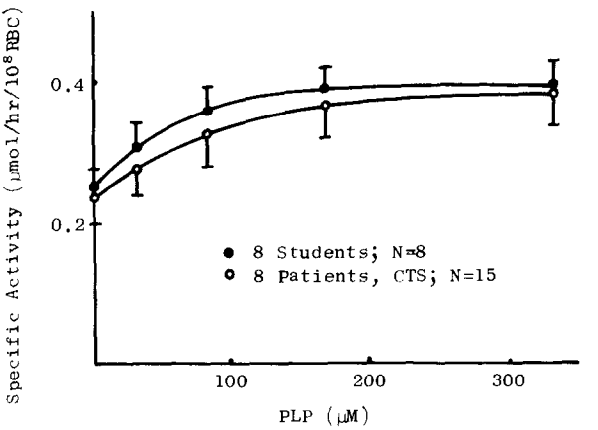

Fig. 1. Activation by PLP of EGOT from University students and from patients with the carpal tunnel syndrome.

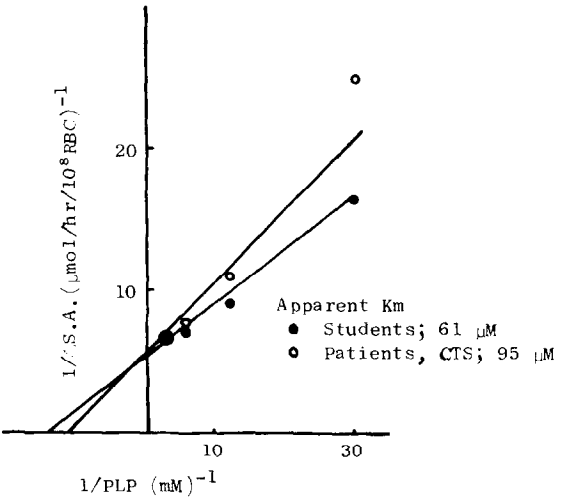

Fig. 2. Evaluation of apparent Km of EGOT for patients with the carpal tunnel syndrome and for University students.

The group of students consisted of 1 male and 7 females, ranging in age from 18 to 28. The group of patients consisted of 5 males and 3 females, ranging in age from 25 to 53. Two of the eight students had mild but distinct symptoms of the carpal tunnel syndrome; 1 male had nocturnal paresthesia in an arm, and 1 female had periodic tingling in the fingers. Each of the eight patients had severe symptoms; parethesias were common. It seems probable that individuals living for years with a high deficiency of vitamin B_6, evidenced by an S.A. in the range of 0.20-0.25, can progress from occasional mild symptoms(as for the two students) to severe symptoms at the age of 40 and older.

ACKNOWLEDGMENT

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