Extraocular Palsy and Thiamine Therapy in Wernicke’s Encephalopathy

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Extraocular muscle palsies in Wernicke’s encephalopathy are attributed to a lack of thiamine (1–3) and usually respond to replacement therapy although the recovery time varies in different subjects (2, 3). It has been suspected that other nutrient deficiency may influence responsiveness. Indeed, recently patients who exhibited no laboratory evidence of a deficiency of this vitamin (4–6) have been reported with eye signs and other features of this condition. The present studies were undertaken to assess further causes for variation in the time period required for eye signs to disappear following thiamine therapy in patients with Wernicke’s encephalopathy. Serial clinical and biochemical studies were obtained before and after receipt of thiamine in seven patients who had a history of chronic alcoholism and who were hospitalized with this condition.

Material and Methods

The patients were males ranging in age from 26 to 55 years. Each had a history of chronic alcoholism with daily consumption of an equivalent of one or more pints of ethanol, in the form of whiskey, wine, and/or beer, for 1 or more months prior to hospitalization. Food intake had been grossly deficient in protein, consisting largely of carbohydrates during several weeks before admission. None had received vitamins prior to admission. Five of the seven patients had one or more episodes of delirium tremens. Each of the patients had bilateral lateral rectus palsy, six had nystagmus, three medial rectus palsy, and one ophthalmoplegia at the time of hospitalization. Mentation was abnormal in each of the patients, five were disoriented, and four exhibited confabulation, euphoria, and memory loss. Six patients had peripheral neuropathy. Hepatomegaly was present in four patients and glossitis in five. There was no clinical or laboratory evidence of cardiac, renal, or pulmonary disease.

Laboratory tests included a complete blood count, urinalysis, serology for syphilis, chest X-ray, bone marrow examination, liver biopsy, and spinal fluid examination. One half of the liver biopsy specimen was incubated in a mixture containing tritiated thymidine (3H) to study in vitro DNA synthesis, and tritiated uridine (3H) to study in vitro RNA synthesis (7). Blood was obtained before therapy for measurement of thiamine (8) and other vitamins, serum magnesium (9), red blood cell transketolase activity (10), serum bilirubin, and serum protein electrophoresis. Vitamins A (11), E (12), and C (13) were measured by chemical tech-
niques; thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin, and vitamin B₁₂ were assayed by protozoological methods, and folic acid by *Lactobacillus casei* (14).

Treatment during the first 24 hr after admission consisted of 10 mg of thiamine given intravenously with food intake restricted to glucose in water. Following receipt of thiamine, blood was drawn at 15, 30, 60, 120, and 240 min and 24 hr for measurement of blood thiamine and red blood cell transketolase. Neurological examination was repeated at 15, 30, and 60 min and 2, 4, 12, and 24 hr after therapy with special attention to oculomotor movements, nystagmus, pupil size, pupillary reaction to light, psychometric testing, and visual field examination.

RESULTS

Five of the seven patients had a blood thiamine of 4–16 ng/ml as compared with a value of 25–50 ng/ml established in healthy controls (8). The remaining two cases had initial thiamine levels of 37 and 32 ng/ml. The red blood cell transketolase activity was between 400 and 550 μg/ml per hour in five of the patients with low circulating levels of thiamine as compared with a value of 950–1,250 μg/ml per hour in healthy controls; transketolase activity was within normal limits in the two patients with normal blood thiamine. In vitro addition of TPP increased the transketolase activity in patients with low blood thiamine but did not alter it in the two patients with normal thiamine (Fig. 1).

Serum magnesium was normal in all patients; serum protein electrophorograms were abnormal in six patients. Low serum levels of folic acid (greater than 20% below the lowest normal level) were present in each of the patients. Serum vitamin B₉ was low in three; riboflavin, nicotinic acid, and B₁₂ in two; and vitamins A and C in one patient. Hematologic studies revealed normochromic normocytic anemia in two patients and macrocytosis with a megaloblastic bone marrow in two. Percutaneous liver biopsies revealed no histologic abnormalities in two patients, moderate fatty metamorphosis in one, fibrosis without lobular distortion in two, and moderate cirrhosis in two. A study of in vitro hepatic nucleic acid synthesis (7) showed normal labeling patterns in the two subjects with normal liver and the patient with fatty liver: increased incorporation of ³HT and ³HU into DNA and RNA, respectively, in 2 patients with cirrhosis; and decreased incorporation of these precursors into nucleic acids in two patients with hepatic fibrosis.

Influence of Therapy

Four hours after thiamine administration there was a disappearance of extraocular palsy and a significant increase in red blood cell transketolase activity in the two patients with a normal liver and the patient with a moderately fatty liver (Fig. 2). Despite correction of a low blood thiamine, extraocular palsy and low transketolase activity persisted for 24 hr in one patient and for 48 hr in another, both of whom had cirrhosis (Fig. 3).

Administration of parenteral thiamine (50 mg daily for 5 days) had no influence on ocular signs in two patients with hepatic fibrosis, a normal pretreatment blood thiamine, and normal red blood cell transketolase. Both of these patients had a serum folic acid of less than 3.5 ng/ml and vitamin B₁₂ of less than 80 ng/ml. A deficiency of DNA synthesis was present, reflected in bone marrow megaloblastosis.
in one of these patients; an elevated level (2.04 mg/100 ml whole blood) (normal, 0.50 to 1 mg/100 ml whole blood) persisted despite thiamine therapy and only returned to normal with improvement in nucleic acid synthesis.

**Response of Other Neurological Abnormalities**

Nystagmus, pupillary inequality, miosis, and sluggish reaction to light decreased over a several-day period after disappearance of ocular palsy. Signs and symptoms of peripheral neuropathy improved less rapidly. Lethargy, apathy, stupor, and, at times, confusion, disappeared over a 24- to 48-hr period; memory loss, confabulation, disorientation, and intellectual loss often persisted for several weeks and progressed in one patient despite a decrease in abnormal neurologic findings.

**DISCUSSION**

The variable response of ophthalmoplegia to thiamine in Wernicke's encephalopathy has been reported previously. Refractoriness is frequently noted when the vitamin is administered orally because of and diminished in in vitro uptake of $^3$HT by percutaneous liver biopsies. A 350-g carbohydrate, 120-g protein diet was given and supplemented with therapeutic amounts of all known vitamins. This regimen led to disappearance of extraocular palsies with correction of hematological changes and deficient hepatic DNA synthesis within 10 days in one patient and within 14 days in the other (Fig. 4). Serial serum pyruvic acid levels (15) were obtained
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decreased gastrointestinal absorption of thiamine in malnourished subjects (16). The variation in time required for response to parenteral thiamine appears to be partly due to the period necessary for conversion of thiamine into its metabolically useful form.

Our observations indicate that the status of the liver is an important determinant of the ability to utilize thiamine. Hepatic disease may interfere with phosphorylation of thiamine (17) and formation of transketolase (18, 19); knowledge of the effects of in vivo and in vitro thiamine on red blood cell transketolase activity may provide information on these processes. Activity of red blood cell transketolase increases with in vivo thiamine or in vitro addition of thiamine pyrophosphate (TPP) in patients without significant hepatic disease, who exhibit prompt recovery of extraocular palsies. Patients with cirrhosis who have no change in transketolase after in vivo thiamine or in vitro TPP show slower recession of the ocular abnormalities.

Further study is necessary to elucidate the biochemical lesion responsible for Wernicke's encephalopathy in patients with normal blood thiamine and red blood cell transketolase activity. A review of our past experience revealed extraocular palsies responded within 48 hr to large doses of parenteral thiamine and other B complex vitamins in 17 of 20 patients with Wernicke's encephalopathy. Eye signs, in the two patients who had prolonged refractoriness to thiamine in the present series, could not be attributed to a deficiency of this vitamin. Ocular palsy only disappeared after several days of a nutritious vitamin-supplemented diet that corrected vitamin B12 and folic acid deficits, restored normal bone marrow morphology, and increased hepatic nucleic acid synthesis. Refractoriness of ocular signs and hyperpyruvatemia to thiamine therapy may have been due to an abnormality of DNA-dependent, RNA-synthetic processes that resulted in deficient production or utilization of pyruvate decarboxylase.

The present investigations emphasize the importance of nutrient deficiencies other than thiamine in malnourished alcoholics with Wernicke's encephalopathy. Patients with classical features of Wernicke's encephalopathy have been observed to have a normal thiamine and red blood cell transketolase (4–6). This condition or peripheral neuropathy occasionally develops in alcoholics despite receipt of supplemental multivitamins containing thiamine. Such patients may exhibit a normal blood and tissue thiamine; in some instances, neuropathy diminishes only when pantothenic acid, nicotinic acid, or pyridoxine deficiency is corrected (20). Progression of mental abnormalities despite correction of extraocular palsy or peripheral neuropathy in patients with Wernicke's encephalopathy may also be due to failure to provide appropriate replacement therapy.

It has been suggested by Pauling (21) that in some persons the cerebrospinal concentration of thiamine or other vital substances may be grossly low at the time the concentration in the blood is essentially normal. He attributes this to physiologic abnormalities such as decreased permeability of the blood–brain barrier for vital substances or increased metabolism of the substance in the brain. Thus, altered DNA-dependent synthesis of enzymes necessary for vitamin transport could produce a localized cerebral deficit and symptoms (16). According to this thesis, one has to consider cofactor requirements for both transport and utilization in analysis of mechanisms (22) responsible for neurologic syndromes seen in malnourished alcoholics with Wernicke's encephalopathy.

CASE REPORTS

Case 1. T.P., aged 26, was hospitalized because of confusion, ataxia, and blurred vision. History revealed the patient had consumed 2–3 quarts of wine daily and had eaten principally carbohydrate-containing foods during the
preceding 6 weeks. He had ingested large quantities of wine since age 17 and had been hospitalized previously for delirium tremens. Examination revealed an enlarged liver, confusion, confabulation, and disorientation. Visual acuity was 20/200, O.U., both optic discs were pale, and there were bilateral central scotomata. Complete bilateral lateral rectus palsies, a partial bilateral medial rectus palsy, and vertical nystagmus were present. The gait was ataxic. Ankle jerks were absent and there was impairment to pin prick, touch, temperature, and vibratory sensation on the lower extremities.

Laboratory studies showed a hematoctit of 48, normal urinalysis, spinal fluid, and serum magnesium. Liver function tests showed abnormal bromsulphalein (BSP) retention, hyperbili- rubinemia, and hypoprothrombinemia. Liver biopsy showed moderately fatty liver with normal in vitro nucleic acid synthetic capacity. Blood thiamine on admission was 14 ng/ml and red blood cell transketolase was 580 µg/ml per hour with an increase to 720 µg/ml per hour with in vitro addition of TPP (Fig. 2). Circulating vitamin levels were normal except for a low serum folic acid.

Recession of extraocular palsies was noted within 2 hr after administration of thiamine; eye movements were completely normal within 4 hr. Six days after admission the patient became delusional and exhibited auditory and visual hallucinations; this state persisted and required eventual transfer to a psychiatric hospital.

Case 2. N.G., 31, was hospitalized because of dysarthria, double vision, and ataxia. History revealed the patient had consumed large quantities of whiskey and beer since age 18. His diet had been inadequate for several months prior to admission. He had previously been hospitalized because of delirium tremens. Examination showed lethargy, confusion, disorientation to time, place, and person, with evidence of impaired memory and comprehension. The pupils were normal. Bilateral lateral rectus palsies and horizontal and vertical nystagmus were present. Gait was ataxic and there was an intention tremor on finger to nose and heel to knee tests. The knee jerks were diminished and the ankle jerks absent. Plantar reflexes were normal. Sensations of pain, touch, and cold were diminished below the knees.

Laboratory studies showed a hematoctit of 44 and normal urinalysis, spinal fluid, and serum magnesium. Liver function tests showed no abnormalities; a liver biopsy was normal. Blood thiamine on admission was 17 ng/ml and transketolase was 470 µg/ml per hour with an increase to 660 µg/ml per hour upon in vitro addition of TPP. Serum folic acid, serum vitamin B₁₂, and blood riboflavin were low.

Disappearance of the lateral rectus palsies occurred 4 hr after the onset of treatment and there was gradual improvement in mentation and peripheral neuropathy during the ensuing 3 months.

Case 3. J.M., 41, was hospitalized because of double vision. He had been admitted previously for delirium tremens. The history indicated that the patient had consumed large quantities of beer and whiskey over a 10-year period. Several months before admission, his appetite decreased and for 2 weeks prior to admission, his total calorie intake was derived from alcoholic beverages. Examination revealed disorientation to time, confabulation, and impairment of recent memory. There was bilateral horizontal and vertical nystagmus, complete lateral rectus palsies, and partial medial rectus palsies. The pupils were normal. A tremor of the tongue was present. The gait was wide based and ataxic and there were bilateral finger to nose and heel to knee ataxia.

Laboratory study showed a hematoctit of 50 and normal urinalysis, serum magnesium, and spinal fluid. Liver function tests and biopsy were normal. On admission, blood thiamine was 4.8 ng/ml and transketolase was 580 µg/ml per hour. Except for a low blood thiamine and serum folic acid other vitamins were within normal limits.

Extraocular palsies disappeared 4 hr after receipt of thiamine and there was decrease of ataxia and mental abnormalities 24 hr after treatment was begun. His neurological abnormalities gradually disappeared on a nutritious vitamin-supplemented diet during the ensuing 6-month period.

Case 4. R.B., 43, was hospitalized because of double vision of several days duration. He had consumed large quantities of wine and whiskey daily and eaten principally carbohydrate foods for several months before admission. Examination revealed evidence of recent weight loss, a smooth and red tongue, confusion, disorientation, and confabulation. There was bilateral lat-
eral rectus palsy, vertical nystagmus, and ataxia. Pupils were miotic. The distal muscles of the lower extremities exhibited atrophy with absent knee and ankle jerks. Plantar reflexes were normal. Sensations of pain and touch were diminished below the knees.

Laboratory studies revealed a hematocrit of 38, macrocytosis on peripheral smear, bone marrow megaloblastosis, and a normal urinalysis, spinal fluid, and serum magnesium. Liver function tests revealed an elevated serum bilirubin and abnormal 45-min BSP retention. A liver biopsy revealed fibrosis, fat, inflammation, 3-labeled nuclei in the liver biopsy specimen incubated with 3HT (over 12 expected) and 2-labeled in the liver biopsy specimen incubated with 3HU (4+ expected). Blood thiamine on admission was 37 ng/ml and transketolase was 1,000 μg/ml per hour with an increase to 1,050 with addition of TPP. Serum folic acid was 3.4 ng and vitamin B12, 60 ng; other circulating vitamins were normal.

Thiamine given in doses of 10 mg intravenously on 2 consecutive days followed by 50 mg intramuscularly each day for 5 days had no influence on extraocular palsy. Initiation of a 300 g carbohydrate, 120 g protein, 100 g fat diet supplemented by therapeutic quantities of B-complex vitamins given parenterally was followed by return of normal serum vitamin B12 and folic acid, disappearance of extraocular palsy, restoration of normal in vitro hepatic DNA and RNA synthesis patterns, and disappearance of bone marrow megaloblastosis 14 days later. Peripheral neuropathy and mental signs decreased slowly over the ensuing 6 months.

Case 5. J.B., 57, was hospitalized because of nervousness and difficulty in walking. History revealed chronic alcoholism with hospitalization on three previous occasions because of delirium tremens. He had ingested large quantities of whiskey and wine and eaten a diet inadequate in protein-containing foods for several months before admission. Examination revealed icterus, glossitis, and hepatomegaly. There were confusion, confabulation, and auditory and visual hallucinations. He had bilateral miosis, lateral rectus palsy, and horizontal and vertical nystagmus. Ankle jerks were absent and associated with truncal and lower extremity ataxia. Sensations of pain, touch, and vibration were diminished below the knees.

Laboratory studies showed a hematocrit of 33, a normochromic normocytic peripheral blood smear, normal urinalysis, normal spinal fluid, and normal serum magnesium. Liver function tests showed abnormal 45-minute BSP retention and elevated serum bilirubin. A liver biopsy revealed active cirrhosis with an increase in in vitro hepatic DNA synthesis. Blood thiamine was 15 ng/ml on admission, red blood cell transketolase was 410 μg/ml per hour with an increase to 600 μg/ml per hour with addition of TPP. Circulating levels of folic acid, vitamin B12, and vitamin A were low.

Extraocular palsies and mental symptoms began to decrease 12 hr after initiating therapy and had disappeared within 24 hr (Fig. 2). Anemia, liver function tests, and peripheral neuropathy gradually improved on a nutritious vitamin-supplemented diet during the ensuing 4-month period.

Case 6. C.B., 54, was hospitalized because of progressive confusion, lethargy, and ataxia. The patient had a long history of heavy alcoholic intake. For several months his daily food intake had consisted of a bowl of soup and two glasses of milk. He had been admitted on two previous occasions because of delirium tremens. Examination revealed ankle edema, hepatomegaly, and glossitis. Lethargy, disorientation, confusion, and confabulation were prominent. There were bilateral lateral rectus palsy, horizontal and vertical nystagmus, and small irregular pupils, which reacted sluggishly to light. The gait was ataxic, ankle and knee jerks were absent, and sensations to pin prick, light touch, cold, and vibratory sensations were decreased below the knees.

Laboratory studies showed a hematocrit of 37, a normochromic and normocytic peripheral blood smear, a normal urinalysis, a normal spinal fluid, and normal serum magnesium. Liver function tests showed abnormal 45-min BSP retention and an elevated serum bilirubin. A liver biopsy showed active cirrhosis with increase in in vitro DNA and RNA synthesis. Thiamine on admission was 10 ng/ml, transketolase 530 μg/ml per hour rising to 800 μg/ml per hour with addition of TPP. Serum folic acid, serum vitamin B12, and blood riboflavin were low; other vitamins were normal.

Extraocular palsy remained unchanged for 48 hr despite administration of thiamine, after which it disappeared rapidly. Peripheral neuropathy, mental alterations, and hepatic status
gradually improved during the ensuing 3-month period.

Case 7. P. Mc., 55, was hospitalized because of blurred vision. The patient had eaten poorly and had consumed large quantities of whiskey and beer during the preceding several years. Examination revealed glossitis, hepatomegaly, and brownish pigmentation over the lower extremities. There was confusion; disorientation to time, place, and person; confabulation; and impaired memory. Bilateral lateral medial rectus palsies were present; the pupils were miotic and reacted sluggishly to light. The gait was broad based and ataxic. Plantar reflexes were normal; knee and ankle jerks were absent. Light touch was diminished below the knees.

Laboratory study showed a hematocrit of 38, macrocytosis, bone marrow megaloblastosis, normal urinalysis and spinal fluid, and an elevated serum globulin. Liver function tests showed abnormal BSP retention; liver biopsy revealed fibrosis, fat, and inflammation with absence of in vitro incorporation of \(^{3}H\)T into DNA and negligible incorporation of \(^{3}H\)U into RNA. On admission, blood thiamine was 32 ng/ml and red blood cell transketolase was 1,100 \(\mu g/\)ml per hour. A serum pyruvic acid was 2.04 mg/100 ml whole blood. Circulating levels of folic acid, vitamin \(B_{9}\), vitamin \(B_{12}\), nicotinic acid, and vitamin \(C\) were low.

There was no change in extraocular palsy following administration of 10 mg of thiamine intravenously on 2 consecutive days followed by 50 mg of thiamine intramuscularly each day for 3 days (Fig. 4). A 300 g carbohydrate, 120 g protein, 100 g fat diet was initiated on the third hospital day and supplemented by therapeutic quantities of B complex vitamins and vitamin \(C\) administered parenterally. This regimen led to a restoration of normal circulating vitamin levels, an increase in in vitro hepatic DNA and RNA synthesis, disappearance of bone marrow megaloblastosis, and restoration of normal levels of serum pyruvic acid (0.68 mg/100 ml whole blood). Improvement in extraocular palsy was first noted on the 9th day of treatment; palsy disappeared on the 10th day of treatment. Within 2 months there was appearance of bone marrow megaloblastosis; decrease of glossitis and peripheral neuropathy; and diminution of confabulation. Periodic disorientation persisted for the ensuing 6 months requiring transfer to a nursing home.

SUMMARY AND CONCLUSIONS

Clinical and metabolic studies revealed considerable variation in the time required for lateral rectus palsy to disappear in seven malnourished alcoholic patients with Wernicke's encephalopathy given parenteral thiamine. Correction of a low blood thiamine caused eye signs to disappear within 4 hr in three patients without significant liver disease, whereas, 24–48 hr were required in two patients with cirrhosis. Occult palsy only decreased after prolonged receipt of a nutritious vitamin-supplemented diet, correction of vitamin \(B_{12}\) and folate deficiency in two patients with bone marrow megaloblastosis, and deficient hepatic nucleic acid synthesis.

REFERENCES

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