OCCURRENCE OF ACUTE WERNICKE'S ENCEPHALOPATHY DURING PROLONGED STARVATION FOR THE TREATMENT OF OBESITY*

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THE more liberal use of prolonged starvation in the treatment of obesity has posed a number of questions regarding the metabolic requirements of body tissues under these conditions. The need for vitamin supplementation has not been studied adequately as yet.

It has been held that total fasting does not result in vitamin B_1 deficiency because vitamin need and vitamin excretion diminish after a few days.[1-3] Ziporin et al.[4] have postulated that thiamine requirements decrease with a lowering of caloric intake. Similarly, it has been noted that thiamine requirements fall with diminishing physical activity.[5] In the starving obese subject endogenous fat and small quantities of amino acids, the equivalent of 4 to 6 gm. of nitrogen per day, are being metabolized by various pathways to provide calories. Therefore, one might expect the need for thiamine to be minimal because this vitamin functions primarily as a coenzyme in the decarboxylation of alpha-ketoacids that arise in the metabolism of glucose derivatives and amino acids. Determinations of the urinary excretion of some of the components of the vitamin B complex have indicated a continued loss during starvation, with the possible depletion of tissue stores.[6,7] Gellene et al.[7] also found low serum levels of vitamins B_1, B_2 and B_6 and pantothenic acid. Nonspecific symptoms such as nausea, vomiting and hypotension were thought to have been ameliorated by vitamin supplementation.

Recently, an acute fulminating thiamine deficiency was observed in an obese man who had starved for a relatively short period. This unusual and unexpected development, to our knowledge, has not previously been described. The circumstances of this case are presented below.

CASE REPORT

M.W., a 35-year-old single truck driver, was admitted to the metabolic-balance ward of the Wadsworth Veterans Administration Hospital on February 16, 1965, complaining of marked overweight resulting in shortness of breath. He had started to gain excessively at the age of 20. Repeated and various reducing regimens in the past had proved ineffective. He claimed to be eating only enough food to satisfy his hunger, but calculations of his dietary record, obtained by the recall method, showed that he was consuming an average of 5600 to 6600 calories daily. His diet consisted of a normal variety of food, including ample meats, dairy products, bread and vegetables, with a calculated intake of thiamine ranging from 2.5 to 3.4 mg. per day. He denied the use of alcohol or drugs. There was no history of exposure to toxic agents, and he had had no significant illness in the past except for mastoid surgery in 1939.

On physical examination the patient was grossly obese, weighing 151.9 kg. (335 pounds) and being 180 cm. tall. The blood pressure was 130/86. No nystagmus was noted, and there was no double vision. The fundi were normal. The lungs and heart were normal. Examination of the abdomen was unsatisfactory because of obesity. The testicles were atrophic. Neurologic examination revealed no abnormalities.

A urinalysis, complete blood count, serum electrolytes and creatinine were within normal limits. The fasting blood sugar was 128 mg., the cholesterol 237 mg., and the uric acid 6.9 mg. per 100 ml. An electrocardiogram and x-ray film of the chest were normal.

The patient volunteered to be included in a group undergoing prolonged starvation as a treatment for "resistant obesity." During the starvation period a special study of vitamin-excretion rates was planned, and, therefore, no vitamin supplements were furnished. A 500-calorie diet was started on February 25. On this regimen, he lost 10 kg. (22 pounds) in 26 days. The starvation period lasted for 30 days (March 21 to April 20) and resulted in an additional weight loss of 17.2 kg. (38 pounds). Only water was permitted. The routine medication consisted of probenecid, 1 gm., and potassium chloride, 2 gm. daily. With starvation ketonemia developed (maximum level of 17.3 mg. per 100 ml.). The serum uric acid rose from 5.6 to 10.2 mg., the blood sugar fell to a low of 69 mg., and the cholesterol decreased to 115 mg. per 100 ml.; the serum sodium, potassium, carbon dioxide and chloride remained unchanged.

The patient did well until April 13 (23 days from the onset of starvation). From April 14 on, he had occasional mild nausea, with emesis, but remained ambulatory and active. On April 20, because of nausea, the fast was terminated, and for the following week, as is done routinely with refeeding, 90 gm. of glucose was administered daily in divided doses by mouth. On the following day, the 1st after termination of the fast, he complained of dizziness, which increased over a 5-day period. Nausea gradually subsided, and on April 28 orange juice was started (6 ounces 3 times daily) in addition to glucose. On May 2, 12 days after refeeding was begun, the patient complained of double vision. He had become inactive, remained in bed and refused to bathe. On May 3 he became highly irritable and unco-operative and complained of double vision and of ringing in the ears. Examination of the eyes on this day for the 1st time revealed a bilateral partial 6th-nerve paralysis. One day later he became incontinent, lethargic and confused; he did not know his age or where he was or the date. On May 5 his memory was more seriously impaired. He was unable to perform the simplest calculations or abstract simple proverbs. He appeared to be extremely dull mentally. The sense of smell was intact on the left but impaired on the right side. The visual fields were intact; the pupils were equal and regular, and the disk margins appeared sharp. There was a clockwise rotatory nystagmus, more severe on the left. Only a 2-mm. horizontal medial eye movement, with no excursion lateral to the midline,

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was discernible. Downward gaze was normal; upward gaze was limited. The patient manifested continuous facial grimacing and teeth gnashing. A partial weakness of the nerves of the left lower part of the face was noted. No abnormalities of the 5th, 8th, 9th, 10th, 11th and 12th cranial nerves were apparent. Motor and sensory perception was normal, as were superficial skin reflexes. The left ankle jerk was absent; Romberg's sign and gait could not be tested. There was no nuchal rigidity and no abnormal toe reflexes.

X-ray films of the skull, an electroencephalogram and a cerebral photoscan using radioactive mercury (Hg^{203}) were within normal limits, as were a complete blood count, urine, serum electrolytes, creatinine, uric acid and cholesterol on the same day. No ketone bodies were present in the serum or urine. No lumbar puncture was carried out, but on the basis of available evidence, a mass lesion or demyelinating disease was considered unlikely. At 5 p.m. on May 5 an intravenous infusion of 1000 ml. of 5 per cent dextrose in water containing 400 mg. of thiamine hydrochloride was started. Improvement was dramatic. By 7 p.m. the patient was sitting up to eat dinner. Another 400 mg. of thiamine hydrochloride was administered during the night. By 3:30 a.m. on May 6 he was completely alert and oriented. Two days later eye movements were fully restored, the mental state was normal, and he was up and about. A 500-calorie diet containing 50 gm. of protein was given, with 1 therapeutic vitamin capsule daily. Some rotatory nystagmus remained, and some diplopia on occasion. He continued to complain of this and a slight unsteadiness when walking. Within 4 weeks after the 1st administration of thiamine chloride all subjective abnormalities had subsided. A trace of rotatory nystagmus could still be elicited 3 months later but all other objective neurologic abnormalities had reverted to normal.

Complete urine collections were carried out before and throughout the starvation period. Thiamine chloride was determined daily.[8] Table 1 demonstrates total B_1 excretion for this subject and 4 other starving patients who did not receive any vitamin supplements. Cases 1 and 2 had been taking a 500-calorie diet before starvation whereas the other 3 had been eating normally and started starvation abruptly. The lower urinary thiamine content during the initial days of starvation in Cases 1 and 2 seemed to reflect the preliminary low-calorie intake.

Discussion

Wernicke's syndrome is characterized by paralysis of extraocular muscles, nystagmus, ataxia and mental changes. Petechial bleeding in the brainstem is found at autopsy. The syndrome and pathological findings have been reproduced experimentally in animals given vitamin-deficient diets.[9] This condition has been noted clinically in patients with chronic alcoholism or malnourishment.[10] In such patients, the paralysis of the eye muscles, the ataxia and the nystagmus were found to clear with administration of thiamine chloride, but little improvement was noted in the mental abnormalities such as impairment of memory and confusion.[11] Therefore, no reliable proof existed for the theory that the thiamine deficiency was responsible for part or all of these mental disturbances. In the case described, the rapid improvement of the mental picture that followed infusion of thiamine seems to furnish evidence that the severe progressive mental deterioration associated with the other typical changes of Wernicke's syndrome can be a sequel of the thiamine deficiency. The failure to find improvement of the mental changes in cases of long standing thiamine deficiency may be due to permanent damage to the structure of the cortex. The cerebral cortex may well be more vulnerable to the harmful effects of the vitamin deficiency than the lower centers in the brainstem. With extensive damage of long duration, specific therapy may therefore be only partially effective. In this case the syndrome developed rapidly, and treatment was begun before permanent cortical changes occurred.

In this patient characteristic symptoms and signs of Wernicke's syndrome did not appear during the starvation period proper, but only after several days of carbohydrate feeding. This is in agreement with the observation of Phillips et al.,[11] who noted accentuation of ocular-muscle paralyses in 6 patients with Wernicke's syndrome after a regimen of glucose and saline solution had been instituted. They suggested that a further depletion of thiamine stores occurred as a result of the added caloric load.

Keys and his associates[12] did not note any vitamin deficiency symptoms in their volunteers on prolonged semistarvation. Gellene's[7] findings, in starving subjects, of nausea, weakness and hypotension were ascribed to thiamine deficiency. However, other metabolic abnormalities known to occur in fasting, such as ketosis, mineral and protein depletion and hyperuricemia, may have been responsible for these symptoms.

In the other 4 starving patients whose vitamin-excretion data were described above, as well as several others in whom vitamin excretion was not measured, no clinical evidence of a thiamine-deficiency syndrome developed during one or more months of fasting or during subsequent refeeding with glucose. This was true regardless of whether starvation was begun abruptly or after a preliminary period on 500 calories. Previously, we had encountered only 1 case in which multiple vitamin deficiencies developed after more than

Table 1. *Urinary Thiamine Excretion during Starvation.*

Calorie Intake*	Thiamine Excretion†							
	5 days before starvation	1-5 days of starvation	6-10 days of starvation	11-15 days of starvation	16-20 days of starvation	21-25 days of starvation	26-30 days of starvation	30 days of starvation
	micro-gm./24 hr.	*micro-gm./24 hr.*	*micro-gm./24 hr.*	*micro-gm./24 hr.*	*micro-gm./24 hr.*	*micro-gm./24 hr.*	*micro-gm./24 hr.*	*micro-gm./24 hr.*
500:								
Case 1	122	54	37	27	20	0	0	0
Case 2	45	22	15	13	5	0	0	0
Ad libitum:								
Case 3	204	156	100	53	43	40	27	0
Case 4	–	175	60	33	31	15	–	–
Case 5	–	180	56	36	28	–	–	–

*Case 1 on this diet for 30, & Case 2 for 20 days; values represent last 5-day period on diet.

†5-day pools.

two months of starvation.[13] However, a history had been obtained suggestive of a poorly balanced diet, high in alcoholic beverages. This may have led to an asymptomatic vitamin depletion before starvation was instituted.

Brin[14] observed no objective characteristic clinical deficiency symptoms in patients given a virtually thiamine-free isocaloric diet for periods up to six weeks. In these subjects physical activity remained constant, and no weight loss was registered for the first three weeks on this regimen. Therefore, thiamine requirements presumably remained constant. Ziporin et al.[4] noted that thiamine excretion ranged around 14 microgm. in twenty-four hours and ceased within eighteen days in subjects fed a thiamine-restricted diet. He concluded that these phenomena indicated a depleted "thiamine status" of a subject. He further calculated the minimum need of an average healthy person as about 270 microgm. of thiamine per 1000 calories. If one assumes that only about 25 to 40 gm. of carbohydrate derivatives are metabolized in the starving person, theoretically, only a fraction of the thiamine requirement of 270 microgm. should be necessary to prevent depletion. During the 500-calorie food-restriction period the daily vitamin intake was about 380 microgm. During the same period nitrogen-balance data indicated daily losses of approximately 100 gm. of protein tissue. Assuming that this tissue contains quantities of thiamine similar to muscle, one could infer that 50 microgm. of thiamine is released daily.[15] Although these combined amounts of dietary and released thiamine seem to be in the range of a theoretically adequate minimum requirement the thiamine-excretion data in the first five-day period of starvation do not seem to support this hypothesis. In comparison with the 3 subjects who ate normally before starvation, the 2 patients on a preliminary low-calorie intake excreted much smaller amounts of urinary thiamine in the beginning of, and throughout, starvation, and the urine was devoid of detectable thiamine after a much shorter period of starvation. By Ziporin's criteria these findings indicated a "depleted thiamine status."

It can be calculated from urinary nitrogen loss that Case 1 metabolized 4.4 kg. of protein tissue during starvation and thus released 2.2 mg. of thiamine, which would provide 73 microgm. of this vitamin per day. An average of 6.9 microgm. per day was measured in the urine, denoting further thiamine depletion.

These data support the conclusion that in the starving or semistarving subject, endogenous release of thiamine does not satisfy tissue needs for this vitamin despite a minimal carbohydrate metabolism. Clinical deficiency manifestations have been shown to develop in 1 patient within one month of starvation.

The variable and unforeseeable responses to starvation in different persons suggest that this treatment regimen should only be carried out in a hospital environment with strict supervision of the patient and that ample vitamin supplementation during starvation is mandatory.

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