

Portal-Systemic Encephalopathy and Hypothalamic Hypothyroidism: Effect of Thyroid Hormone on Ammonia Metabolism

Seiji HITOSHI, Yasuo TERAOKA and Manabu SAKUTA

We describe a 53-year-old woman with portal-systemic encephalopathy and altered thyroid function. Endocrinological studies revealed low levels of free thyroid hormone with an inappropriately low level of thyroid-stimulating hormone that responded to bolus injection of thyrotropin-releasing hormone with a normal but somewhat delayed pattern. On the diagnosis of hypothalamic hypothyroidism, she was treated with levothyroxine sodium. Thyroid hormone replacement improved not only the symptoms of hypothyroidism but the hyperammonemia and consciousness disturbance, which suggested a hitherto undescribed possibility that hypothyroidism may be an exacerbation factor of hyperammonemia and portal-systemic encephalopathy.

(Internal Medicine 32: 655–658, 1993)

Key words: euthyroid sick syndrome, MRI

Introduction

The euthyroid sick syndrome refers to an alteration of thyroid function that occurs in patients with various nonthyroidal illnesses including starvation, infection, and chronic liver disease (1, 2). Patients with the euthyroid sick syndrome have a low serum triiodothyronine (T_3) and sometimes low thyroxine (T_4) with an inappropriately low level of thyroid-stimulating hormone (TSH), but are thought to be clinically euthyroid and need no thyroid hormone therapy (3). There is, however, the possibility that hypothalamic hypothyroidism is overlooked in such patients.

Hypothalamic hypothyroidism is a rare disease; most the cases are associated with overt hypothalamic lesions (4–8). No case of this disease has been reported to be complicated with portal-systemic encephalopathy, although the hypothalamus is the region affected in portal-systemic encephalopathy (9). Moreover, the influence of thyroid hormone on ammonia metabolism and portal-systemic encephalopathy was not fully understood. We present a case with portal-systemic encephalopathy and hypothalamic hypothyroidism whose encephalopathy improved after thyroid hormone replacement.

Case Report

A 53-year-old woman was admitted to our hospital because

of slow speech, which started 2 years previously. She felt unsteady to walk and fell down several times in the 6 months before admission. At another hospital, she had undergone splenectomy and blood transfusion 10 years earlier because of severe anemia. She consumed no alcohol. On physical examination, her general condition was rather well. Myxedema rather than pitting edema was noticed in both legs. On neurological examination, she was alert and mildly demented. Her speech was slow and slightly explosive. There was a diffuse increase in muscle tone in all extremities, but no weakness. Jaw jerk reflex and deep tendon reflex were increased, and Babinski sign was observed in both feet. On finger-to-nose test and heel-to-knee test, dysmetria and decomposition were observed. Her gait was wide based. There was asterixis in both arms.

Laboratory studies showed the following abnormal values: total protein 53 g/L (albumin 26 g/L and globulin 27 g/L), total bilirubin 24 μ mol/L (normal range, 2–18 μ mol/L), prothrombin time 14.3 seconds with a control of 11.0 seconds, hepaplastin test 65% (70–130%), ammonia 92.8 μ mol/L (5–50 μ mol/L), indocyanine green clearance test 37.2% remains after 15 minutes (<10%), and Fischer ratio 1.08 (2.6–4.5). Other data, including aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), electrolytes and blood sugar, were within normal limits. Antibodies and antigens for hepatitis B virus and antibody for hepatitis C virus were all negative. Abdominal ultrasonography and CT scan revealed atrophic and

From the Department of Neurology, Japanese Red Cross Medical Center, Tokyo

Received for publication December 14, 1992; Accepted for publication July 28, 1993

Reprint requests should be addressed to Dr. Seiji Hitoshi, the Department of Neurology, Institute for Brain Research, Tokyo University School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan

nodular liver which was compatible with liver cirrhosis. Liver scintigraphy also showed the liver atrophy without a focal defect. No varix was observed on fiberoptic gastroscopy. Endocrinological studies showed the following values: thyroxine-binding globulin 167 nmol/L (150–360 nmol/L), T_3 0.77 nmol/L (1.2–3.4 nmol/L), free T_3 2.5 pmol/L (4.6–8.9 pmol/L), reverse T_3 0.16 nmol/L (0.29–0.58 nmol/L), T_4 33.5 nmol/L (51–142 nmol/L), free T_4 5.28 pmol/L (10–36 pmol/L), TSH 0.5 mU/L (0.4–4.3 mU/L), and prolactin 19.4 μ g/L (1.4–14.6 μ g/L). TSH and prolactin responded to the bolus injection of 500 μ g of thyrotropin-releasing hormone (TRH), and TSH showed a normal but somewhat delayed pattern (Fig. 1). Other pituitary hormones and cortisone were within normal limits and responded well to a bolus injection of luteinizing hormone-

releasing hormone and insulin. Electroencephalography showed diffuse slowing with δ wave and an occasional triphasic wave. Magnetic resonance (MR) T1-weighted image coronal section of the brain at the level just oral to the mammillary body revealed a high intense area including the globus pallidus and a part of the hypothalamus (Fig. 2). She was diagnosed as having portal-systemic encephalopathy and hypothalamic hypothyroidism.

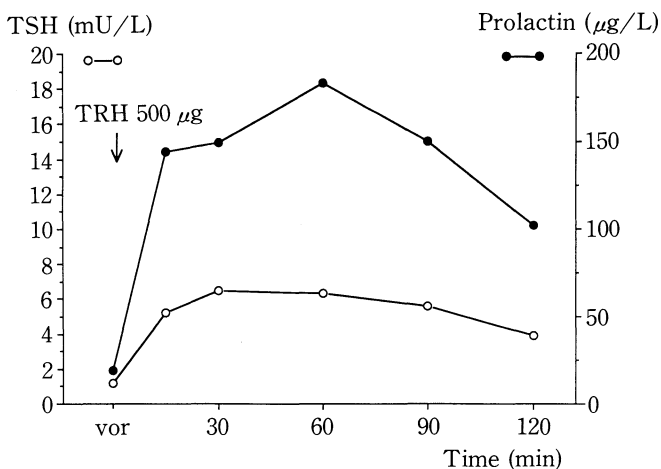


Fig. 1. Thyrotropin-releasing hormone (TRH) tolerance test. Both thyroid-stimulating hormone (TSH) and prolactin responded to 500 μ g of TRH, and TSH showed a normal but somewhat delayed pattern.

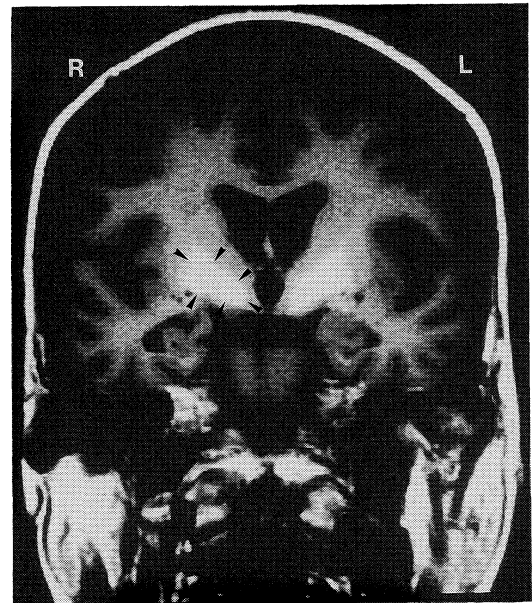


Fig. 2. MRI T1-weighted coronal section just oral to the mammillary body. High intense area was observed in the globus pallidus and in a portion of the hypothalamus (spin echo method, TR=630 msec, TE=20 msec, 1.5T).

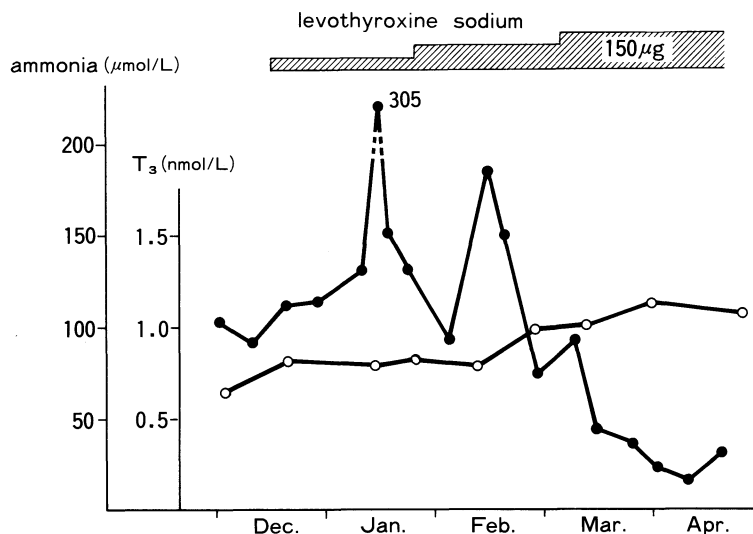


Fig. 3. Clinical course showed a decline in serum ammonia levels (closed circles) after thyroid hormone replacement and increase of serum triiodothyronin (T_3) levels (open circles).

First, protein restriction and the administration of branched-chain amino acids and lactulose were started. Bowel movements were maintained at three to six times a day by laxatives. Nevertheless, her consciousness sometimes fell into the comatose state, accompanying the marked elevation of serum ammonia levels. Thyroid hormone replacement with levothyroxin sodium was then started. After she received 150 µg/day of levothyroxin sodium, the serum T₃ and T₄ levels increased to almost within the normal range. Since then, the serum ammonia value decreased to within normal range under 50 µmol/L (Fig. 3), and her consciousness has remained alert. Laboratory data, including ASAT, ALAT, bilirubin, prothrombin time and hepaplastin test, was almost unchanged throughout the course. Slight increases of albumin (from 26 to 29 g/L) and cholinesterase (from 390 to 470 U/L) were observed. No infection was manifested.

Discussion

Clinical manifestations (consciousness disturbance, pyramidal sign, parkinsonism, ataxia, and flapping tremor) and laboratory data (hyperammonemia and retard indocyanine green clearance) in this patient, together with imaging studies were compatible with liver cirrhosis and the characteristic electroencepharogram indicated portal-systemic encephalopathy. Moreover, the abnormal thyroid function test (low T₃ and T₄) and inappropriately low TSH level suggested the possibility of this patient to have euthyroid sick syndrome or a hypothyroid state of the central type. After bolus TRH injection, TSH responded with a normal but slightly low peak pattern, which was compatible with both euthyroid sick syndrome and hypothalamic hypothyroidism (1, 10). Diagnosis of hypothalamic hypothyroidism is often difficult, because the laboratory data of thyroid function of this disease resemble euthyroid sick syndrome which is sometimes observed in liver cirrhosis. Euthyroid sick syndrome patients with chronic liver disease may display decreased free T₃ and total T₄, but usually have modest elevations in reverse T₃ and free T₄ (1). In the present patient, endocrinological studies revealed a low level of free T₃, together with low levels of reverse T₃ and free T₄. Moreover, the patient was not critically ill but in a rather good state, and had symptoms of hypothyroidism, myxedema. We concluded that she had hypothalamic hypothyroidism.

In euthyroid sick syndrome, thyroid hormone replacement is not thought to be beneficial (3). Portal-systemic encephalopathy patients with low T₃, T₄ and inappropriately low TSH have generally been regarded as euthyroid sick syndrome, and were not considered for further investigation and thyroid hormone replacement therapy. Among them, some might have hypothalamic hypothyroidism like the patient in this study. Levothyroxin sodium in our patient not only relieved the symptoms of hypothyroidism but improved hyperammonemia and portal-systemic encephalopathy, which suggested a possibility that hypothyroidism may be an exacerbation factor of hyperammonemia and portal-systemic encephalopathy.

There has been no clinical report about the effect of thyroid

hormone on portal-systemic encephalopathy and ammonia metabolism in our review of the literature. Also the influence of thyroid hormone on enzymatic activity is not completely understood. Protein synthesis is known to be decreased in hypothyroidism (11). Urea production and activities of urea cycle enzymes, the major metabolic pathway of ammonia, were reported to be increased in hypothyroid rats, indicative of a greater production of ammonia (12–14). Moreover, liver dysfunction might repress or modify the induction of liver enzymes including the urea cycle by thyroid hormone, which would result in the greater production and lesser utilization of ammonia, that is, hyperammonemia. No report described the effect of thyroid hormone on urea cycle enzymes in the dysfunctioning liver.

Hypothalamic hypothyroidism has been reported to be caused by various etiologies, such as tumor (4), irradiation (5), trauma (6), depression (7), and unknown causes (8), but not by portal-systemic encephalopathy. Abnormal high signal intensity of lenticular nucleus and hypothalamus on MR T1-weighted image in our patient was thought to be the result of portal-systemic encephalopathy because a similar abnormality in lenticular nucleus, internal capsule, and hypothalamus was recently reported in patients with this disease (15). The abnormal high intensity on MR T1-weighted image was supposedly caused by the accumulation of heavy metals or fat, of which we thought the latter was more probable. Although the pathogenesis is not clear, this abnormality might influence the activity of hypothalamic neurons and result in hypothalamic dysfunction. The present patient was a very rare case with portal-systemic encephalopathy and hypothalamic hypothyroidism.

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