



## Case Report

## Reversible Leukoencephalopathy Due to Cobalamin Deficiency After Subtotal Thyroidectomy for Graves' Thyrotoxicosis

Chih-Yuan Lin, Yue-Loong Hsin, Wen-Long Tsao\*

Department of Neurology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan

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### Abstract

We report a woman aged 37 years who showed rapid deterioration of psychomotor functions 6 months after a subtotal thyroidectomy for Graves' thyrotoxicosis. In addition to cobalamin deficiency, we observed pathologic changes in the brain tissue in accordance with a white matter disorder on brain imaging. The neurologic deficits and leukoencephalopathic changes in brain imaging responded to cobalamin replacement and returned to normal 6 months after treatment. The relationship between thyroid dysfunction and cobalamin levels in maintaining white matter is briefly reviewed. (*Tzu Chi Med J* 2009;21(1):85–88)

\*Corresponding author. Department of Neurology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, Taiwan.

E-mail address: wenlong1109@hotmail.com

## 1. Introduction

Cobalamin (vitamin B12) and thyroid hormone play significant roles in regulating central metabolic pathways (1,2). The integrity of nerve myelin requires adequate levels of cobalamin as a cofactor for myelin phospholipid methylation, closely related to the serum levels of homocysteine and methylmalonic acid. Moreover, thyroid hormone plays a fundamental role in regulating oligodendrocyte development (2). Hyperthyroidism has been associated with increased oxidative stress (3) and necrotic neuron death (4). In unique conditions, overt thyroid function may influence homocysteine levels and cobalamin function (5). Here, we report the case of a woman aged 37 years who developed symptoms of thyrotoxicosis and then 6 months after her thyroidectomy, developed white matter disease. Her blood cobalamin level was exceptionally

low. Cobalamin replacement improved the impaired neurobehavioral function of the patient.

## 2. Case report

A non-vegetarian housewife aged 37 years was admitted with subacute onset of progressive deterioration of ambulatory, linguistic and cognitive functions occurring over a period of 1 month. Her history revealed no cognitive dysfunction, mental illness, hypertension, stroke, migraine, uremia, central nervous system infection or familial hereditary leukodystrophy, and she had no history of substance abuse. There was also no history of intake of vitamin supplements. She had been continually medicated with famotidine (one tablet 20mg twice daily) for erosive gastritis and a duodenal ulcer for about 2 years. She had been diagnosed

with Graves' disease 2 years previously and had poor methimazole and propylthiouracil medical compliance. Six months prior to the development of neurologic dysfunction, she received a subtotal thyroidectomy for poorly controlled Graves' thyrotoxicosis. At that time, her blood levels were: T3 > 600 ng/dL (reference range, 80–220 pg/mL), T4 > 24 ng/dL (reference range, 4.5–12.5 ng/mL), and thyroid-stimulating hormone 0.007  $\mu$ U/mL (reference range, 0.4–4.0  $\mu$ U/mL). After surgery, the patient had shown transient hypothyroidism (T3, 62.3 ng/dL; T4, 4.63  $\mu$ g/dL; TSH, 6.60  $\mu$ U/mL) for 3 months. She did not receive thyroxine supplementation for her hypothyroidism.

On admission, the patient was wheelchair-bound, could open her eyes spontaneously, and was inattentive, unresponsive to verbal stimuli and unaware of micturition and defecation. Her pupils were 3 mm in diameter and reactive, and the fundi were normal. Eye movements were conjugate. Corneal reflexes were present bilaterally. The face was symmetrical. All four limbs withdrew from noxious stimulation and she had normal tendon reflexes. No Babinski's or Hoffmann's signs were demonstrated. It was difficult to evaluate proprioceptive sensory tests for depressed mental status. Her complete blood count (hemoglobin, 12 g/dL; hematocrit, 37%; mean corpuscular volume, 88.1 fL), urine toxicology and drug abuse screen were unremarkable, and rapid plasma regain, human immunodeficiency virus, antinuclear antibodies, Sjögren antibodies and metabolic screening including BUN/creatinine, glucose, electrolytes, and liver function were all within normal limits. With the exception of a low cobalamin level (176 pg/mL (reference range, 193–982 pg/mL)), no other biochemical or serological abnormalities or infectious indicators were detected. Electroencephalography showed a mix of diffuse theta

and slow alpha frequencies. The results obtained from cerebrospinal fluid analysis showed no abnormalities on cytology, staining, and bacterial and tuberculosis cultures. Antibodies to parietal cells were not observed. T2 fluid-attenuated inversion recovery brain magnetic resonance imaging (MRI) revealed high signal intensity in the bilateral fronto-temporal-parietal subcortical regions and in the corpus callosum (Fig. 1). No apparent abnormality was observed in the spine on MRI. The unusual confluent white matter abnormalities on MRI were confirmed by a stereotactic brain biopsy. The sampled tissue showed multifocal demyelination and vacuolization (Fig. 2).

The patient was treated with hydroxocobalamin, 1 mg intramuscular injection daily for 10 days. After 3 weeks of hospitalization, the patient could respond slowly to speech with simple words and walk with assistance. At this time, her *Mini-Mental State Examination* score was 15/30, with poor performance mainly in time orientation, language, attention and calculation. She was discharged to home care and received outpatient rehabilitation. One month later, the patient appeared to be more alert on her outpatient visit. Five months later, she had recovered and was assessed as being in a normal neurobehavioral state. The white matter abnormalities appeared almost undetectable on MRI scans performed at the 6-month follow-up (Fig. 3). At this time, her thyroid function and cobalamin levels were within the normal ranges.

### 3. Discussion

Cobalamin deficiency undoubtedly resulted in alteration of cognition in this patient, but coexistence of thyroid dysfunction could also have contributed to the

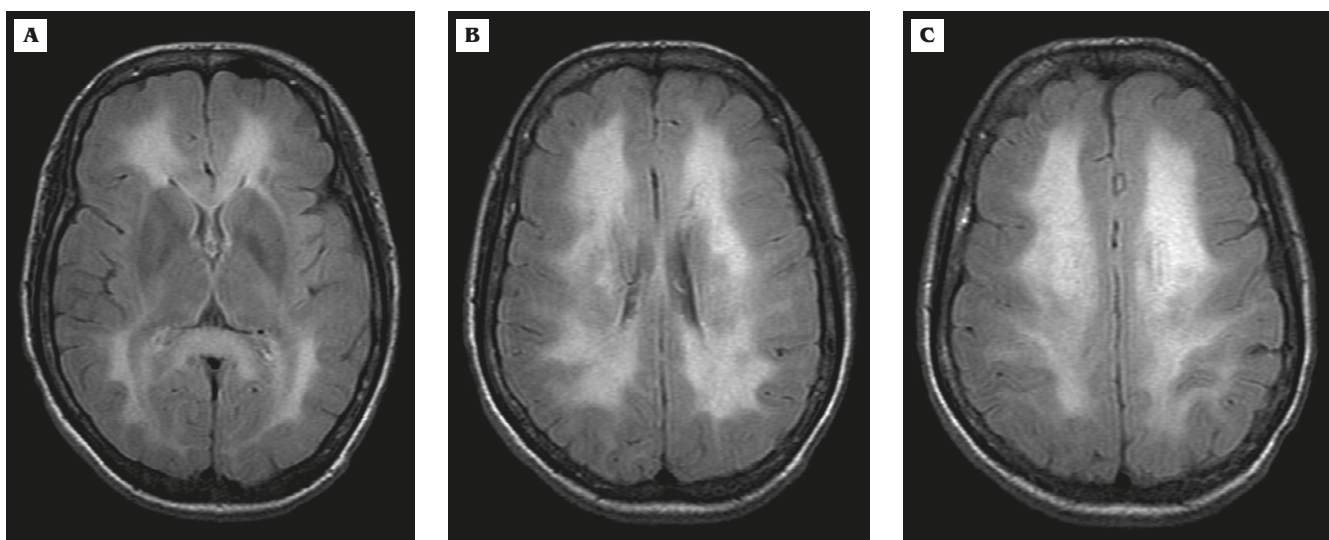
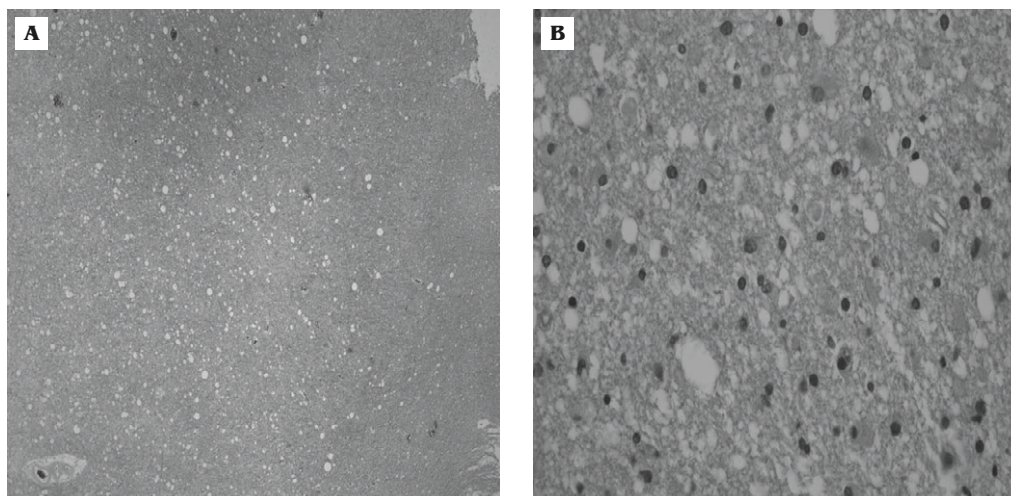
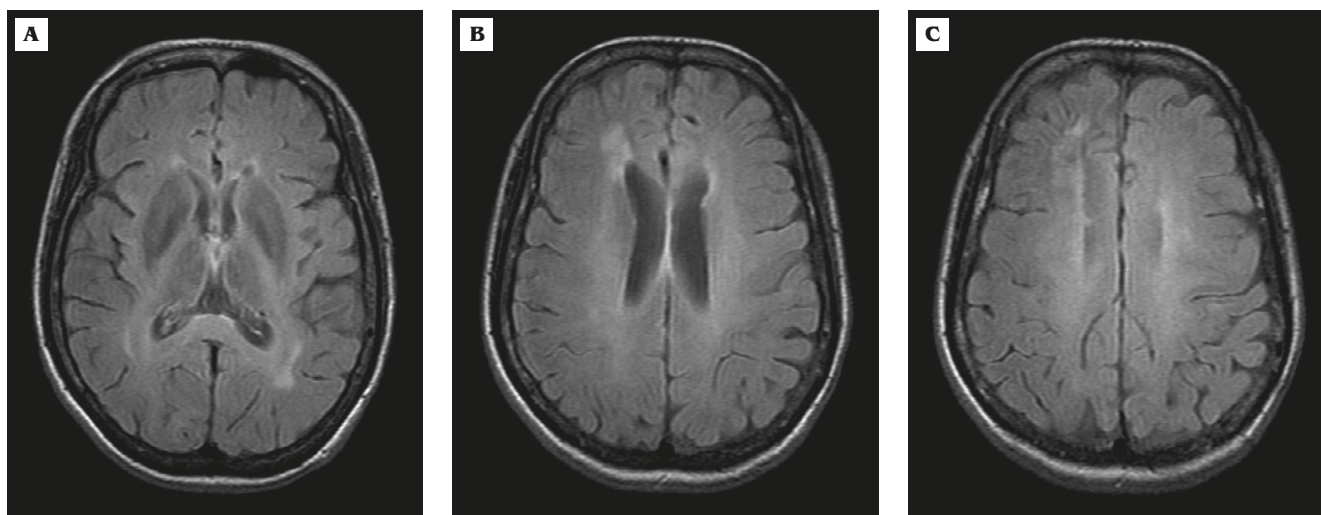


Fig. 1 — T2 fluid-attenuated inversion recovery brain magnetic resonance imaging shows bilateral white matter changes.



**Fig. 2 — Brain biopsy with hematoxylin and eosin staining reveals diffuse white matter vacuolization with gliosis and myelin sheath swelling: (A) 100 $\times$ ; (B) 200 $\times$ .**



**Fig. 3 — At the 6-month follow-up, T2 fluid-attenuated inversion recovery brain magnetic resonance imaging shows partial resolution of white matter changes after 10 doses of hydroxocobalamin (1 mg intramuscular injection).**

leukoencephalopathy. The patient experienced transient hypothyroidism following a subtotal thyroidectomy and administration of propylthiouracil. The subsequent development of cognitive disorders was treated successfully by discontinuing propylthiouracil and administering hydroxocobalamin.

Patients with uremia (6), eclampsia (7), malignant hypertension (8), collagen vascular disorders (9), thrombotic thrombocytopenic purpura (10) and amyloidosis (11), or those receiving immunosuppressants are at risk of developing reversible leukoencephalopathy. These diseases and pharmaceutical agents are capable of disrupting the integrity of white matter, in turn influencing psychomotor processing speed. Patients present with attention deficits, executive dysfunction,

memory-retrieval deficits, visuospatial impairment, and linguistic dysfunction. Analysis of the cobalamin level is routinely performed in patients presenting with dementia, but imaging or pathology studies of the human brain are rarely reported. Chatterjee et al (12) were the first to demonstrate brain pathology in a patient with cobalamin deficiency. The white matter vacuolization with gliosis and myelin sheath swelling described by Chatterjee et al were consistent with the microscopic findings of the sampled brain tissue from our patient.

The pathogenesis of the diffuse myelin and axonal abnormalities associated with cobalamin deficiency and thyroid dysfunction is not well understood. However, it is well documented that cobalamin and thyroid



hormone are required for normal axonal myelination (2). Cobalamin as a cofactor participates in two enzymatic reactions in humans. First, it is a cofactor for the conversion of homocysteine to methionine, an essential requirement for DNA synthesis and maintenance of the myelin sheath by methylation. Second, it is necessary for the conversion of methylmalonyl-CoA to succinyl-CoA. In states of cobalamin deficiency, homocysteine and methylmalonic acid levels rise in the blood. In addition, elevated methylmalonic acid may competitively inhibit succinate dehydrogenase (an enzyme essential for mitochondrial aerobic glucose oxidation) causing mitochondrial dysfunction, or may be incorporated abnormally into branched-chain fatty acids, resulting in abnormal myelination (13). Colleran et al (5) reported that vitamin B and folate deficiencies, in association with thyrotoxicosis, may be risk factors for hyperhomocysteinemia and subsequent thromboembolic events. However, the serum cobalamin level did not differ in a hyperthyroid or hypothyroid state (14). Thyrotoxicosis may be associated with hyperhomocysteinuria and functional cobalamin deficiency (3). In addition, methylenetetrahydrofolate reductase expression is decreased in hypothyroidism (15), and therefore may result in decreasing remethylation and renal excretion of homocysteine. The abnormal myelination and elevated homocysteine cause atherosclerotic effects (16), inadequate cerebral perfusion, necrotic neuron damage and mitochondrial dysfunction, which may contribute to white matter change. The timeline of hyperthyroidism, subsequent hypothyroidism and altered cobalamin levels may correlate with the appearance of neurologic disturbances. However, despite the abnormal cobalamin level identified in our patient, no noticeable abnormalities were observed following endoscopy and colonoscopy studies, and no antiparietal cell antibodies were detected. We acknowledge some limitations in our case report. We could not perform a Schilling test to demonstrate the underlying cause of cobalamin deficiency. In addition, we did not measure homocysteine and methylmalonic acid before cobalamin replacement, which would have better clarified their interrelationship.

Cobalamin deficiency is not uncommon in elderly people with gastric problems, in patients with long-term use of proton pump inhibitors, or in individuals observing a strict vegetarian diet without vitamin supplementation. There is about a 12-month window of opportunity for cognitive recovery with cobalamin replacement (17). Clinicians should consider subtle cobalamin deficiency and thyroid functional states when evaluating a wide range of cognitive and neuropsychiatric symptoms for early detection and treatment of patients with leukoencephalopathy (12). Further study of the interaction between thyroid function, cobalamin, folate, methylenetetrahydrofolate reductase, methylmalonic acid and homocysteine with cognitive

function and white matter change is warranted to better understand the central metabolic pathways.

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