A woman with thyrotoxicosis- and hyperemesis gravidarum-associated Wernicke's encephalopathy

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Abstract

Although hyperthyroidism arising from primary thyroid disease is rare in pregnancy, transient gestational hyperthyroidism is not uncommon. This condition can be associated with hyperemesis gravidarum (HG), and Wernicke's encephalopathy. We present the case of a woman with toxic nodular goiter complicating HG-associated Wernicke's encephalopathy.

A 38-year-old Caucasian woman, who had received a diagnosis of hyperthyroidism and HG early in her pregnancy, had intrauterine fetal death at Week 16 of gestation. One day after undergoing therapeutic abortion, she was admitted to our clinic with persistent thyrotoxicosis, nausea, and vomiting. A toxic thyroid nodule was detected. She was given antithyroid medication, total parenteral nutrition. On Day 10 of hospitalization, she developed ataxia, aphasia, and somnolence. Cranial magnetic resonance imaging showed increased bilateral thalamic signalization. She was given a diagnosis of Wernicke's metabolic encephalopathy, for which she received thiamine and multivitamin preparations. She responded dramatically on the second day of thiamine therapy. Her consciousness improved rapidly and she began to speak. Her muscle tone was slightly weak and she had paresthesias in both legs.

Absorption of thiamine may be particularly impaired in pregnant women with hyperemesis and hyperthyroid disease. Wernicke's encephalopathy should be considered in hyperthyroid women with HG who develop neurological abnormalities.

Abbreviations:

HG	- hyperemesis gravidarum
TSH	- thyroid-stimulating hormone
T4	- free thyroxine
T3	- free triiodothyronine
HCG	- human chorionic gonadotropin
MRI	- magnetic resonance imaging
FLAIR	- fluid-attenuated inversion recovery
GABA	- γ-aminobutyric acid
AIDS	- acquired immunodeficiency syndrome
TSHR	- thyroid-stimulating hormone receptor

CASE REPORT

INTRODUCTION

Hyperthyroidism arising from primary thyroid disease is rarely seen in pregnancy. Transient gestational hyperthyroidism, however, is often associated with hyperemesis gravidarum (HG) (Lazarus 2005), which is defined as persistent vomiting that causes weight loss exceeding 5% of prepregnancy weight, dehydration, and ketonuria (Werberg *et al.* 2005). About 30% to 60% of patients with HG have thyrotoxicosis (Al-Yatama *et al.* 2002). HG is also among the leading nonalcoholism-related causes of Wernicke's encephalopathy, which results from by thiamine deficiency (Wilson *et al.* 2005). We describe the case of a woman with toxic nodular goiter and HG complicated by Wernicke's encephalopathy.

CASE REPORT

A 38-year-old Caucasian woman was referred to our department for thyrotoxicosis, 1 day after undergoing therapeutic abortion for intrauterine death of the fetus. She was at Week 16 of her pregnancy. She had received the diagnosis of thyrotoxicosis early during her pregnancy and had been prescribed propylthiouracil (50 mg three times daily). However, she also had severe nausea and vomiting and could not keep food or medications down from the beginning of the pregnancy. She was given a diagnosis of HG and was given intravenous dextrose solution for nourishment. She was otherwise healthy and had a negative family history. Upon examination, she was oriented and cooperative but had a depressed and occasionally apathetic mood.

Her nausea and vomiting continued upon arrival in our department. She had thyrotoxicosis, with laboratory results as follows: thyroid-stimulating hormone (TSH), 0.01 µIU/mL (normal range, 0.35–5.5 µIU/mL); free thyroxine (T4), 2.38 ng/dL (0.89–1.76 ng/dL); free triiodothyronine (T3), 2.9 pg/mL (2.3–4.2 pg/mL); thyroid antibodies, negative; antithyroglobulin antibodies, 17 U/mL (0–60 U/ml); and antimicrosomal antibodies, 37 U/mL (0–60 U/ml). She also had elevated liver function tests: aspartate aminotransferase, 197 U/L (0–34 U/L); alanine aminotransferase, 305 U/mL (0–49 U/L); total bilirubin, 2.67 mg/dL (0.3–1.2 mg/dL); direct bilirubin, 1.3 mg/dL (0–0.2 mg/dL). She had severe hypokalemia [1.9 mEq/L (3.5–5.1 mEq/L)], anemia [hemoglobin, 10.4 g/dL (11.5–17 g/dL)], hypocalcemia [8.1 mg/dL (8.3–10.6 mg/dL)], ketonuria [150 mg/dL (0 mg/dL)], leukocytes in her urine, and mildly elevated serum C-reactive protein [9.83 mg/dL (0–0.5 mg/dL)]. To exclude the possibility of residual placental tissue retained after therapeutic abortion, we measured the serum human chorionic gonadotropin (HCG) level 7 days after the procedure; this was found to be 253 mIU/mL, revealing a decreasing trend.

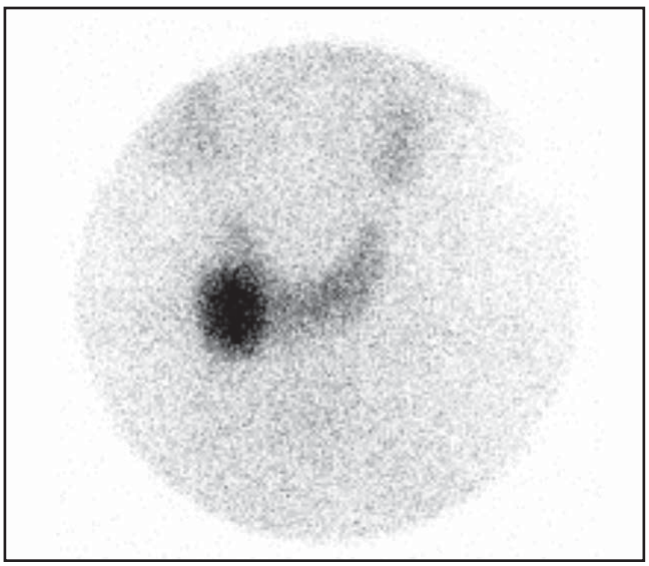

Fig. 1. Thyroid scintigraphy at baseline revealed accumulation in the left lobe compatible with a hot nodule and suppression in other thyroid areas.

Thyroid scintigraphy revealed a solitary, toxic adenoma suppressing the remaining thyroid tissue (Figure 1). In thyroid ultrasonography, the parenchyma was otherwise homogenous; there was a solitary thyroid nodule.

She was given potassium chloride, magnesium, calcium, proton pump inhibitor and metoclopramide intravenously. She was started on methimazole 5 mg twice daily. Because she could not eat despite this therapy, she began receiving a parenteral nutrition solution containing carbohydrates, lipids, and amino acids (Oliclinomel®). We started ceftriaxone empirically after finding leukocytes in the urine; her urine culture was later found to be negative.

On the fifth day, we performed an upper endoscopy to see whether there was a physical cause of her inability to eat or drink. Linear erosions were present at the surface of distal esophagus. We believed these to be the result, not the cause, of the severe nausea and vomiting and continued to give her proton-pump inhibitors. Abdominal ultrasound revealed Grade 1 hepatosteatosis and cholelithiasis. Her liver function tests had started to decrease gradually and eventually returned to normal.

On the tenth day of hospitalization, she underwent a psychiatric consultation and received a diagnosis of posttraumatic stress disorder. For this condition, she was prescribed olanzapine, clonazepam, and paroxetine. She received one dose of olanzapine (2.5 mg) and one dose of clonazepam (0.625 mg) before bedtime. A few hours later, she developed ataxia, aphasia, and somnolence. She was transferred to the intensive care unit, and within hours, she was in deep sedation and lethargic.

The psychiatric drugs were stopped, and a neurology consultation was made. In neurological examination, she opened her eyes only in response to painful stimulation, was uncooperative, and did not obey commands. We observed decreased deep-tendon reflexes without pathologic reflexes. Neck stiffness was absent. Ophthalmological examination revealed rapid rotary

nystagmus, especially on horizontal gaze. Her pupils were round and equal, and both light reflexes were prompt. Electroencephalography yielded normal results. Cranial magnetic resonance imaging (MRI) and venography were performed to exclude sinus thrombosis, given that she had a history of pregnancy and therapeutic abortion. MRI venography was normal. Cranial MRI (T2-weighted images) showed an increased fluid-attenuated inversion recovery (FLAIR) signalization in the medial thalamic regions bilaterally, mammillary bodies, periaqueductal gray matter, and wall of the third ventricle. Restricted diffusion was not detected by diffusion-weighted imaging (Figure 2).

We diagnosed Wernicke's metabolic encephalopathy and prescribed thiamine (100 mg/day) and multivitamin preparations. She responded dramatically on the second day of thiamine therapy. Her consciousness improved rapidly and she began to speak, although she was confusing at times. Her voluntary muscle tone was weak and she had paresthesias in the legs. After 10 days of thiamine treatment, repeat MRI showed nearly total resolution of pathologic signals (Figure 3).

DISCUSSION

Wernicke's encephalopathy is classically characterized by mental confusion, ophthalmoplegia, and ataxia (Wilson *et al.* 2005; Donnino *et al.* 2007). After Carl Wernicke described the disease as a trio of symptoms consisting of drowsiness, ophthalmoplegia, and ataxia in 1881 (Wernicke 1881), Caine *et al.* proposed an operational definition stating that any two of the following four conditions should be sufficient for a presumptive diagnosis: nutritional deficiency, ocular findings, ataxia, and mental status changes (Caine 1997). Our patient met all of these criteria.

The prevalence of disease is about 2% (Torvik 1991), however, only about 15% of these are diagnosed before death (Torvik 1991; Harper *et al.* 1998; Naidoo *et al.* 1996). In autopsy studies, the prevalence has been found to be 0.8%–2.8%, which suggests that most cases remain undiagnosed (Naidoo *et al.* 1996; So&Simon 2004). The long diagnostic time course of our patient's case supports this concept.

Thiamine, also known as vitamin B1, is a water-soluble nutrient obtained through the diet. It is a cofactor for carbohydrate metabolism. The central nervous system uses thiamine to metabolize glucose, maintain myelin, and synthesize acetylcholine, γ-aminobutyric acid (GABA), and glutamate (Victor 1989). Thiamine deficiency therefore can result in tissue injury via inhibited metabolism in regions of the brain that have high metabolic requirements and/or high thiamine turnover (Wilson *et al.* 2005; Donnino 2007; Victor 1989). The mean daily requirement for thiamine is 0.5 mg/1000 kcal in a normal diet (Wilson 2005).

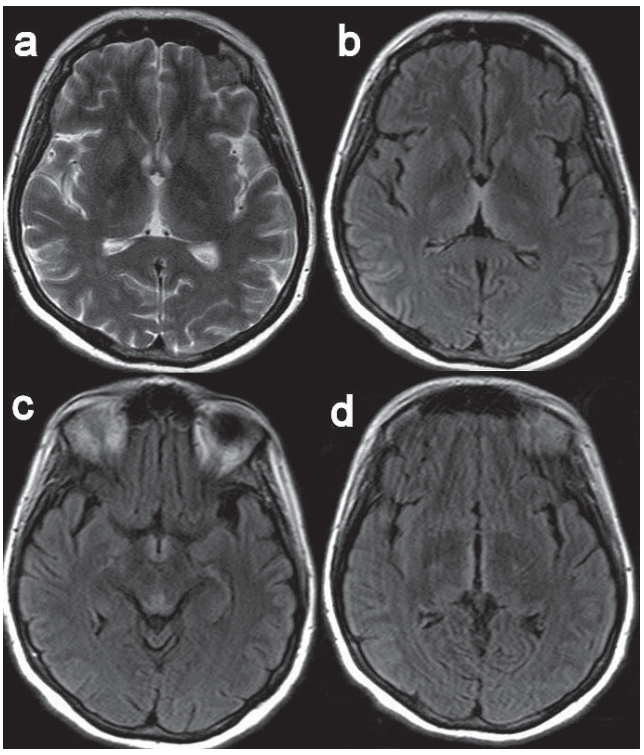

Fig. 2. Axial fluid-attenuated inversion recovery (FLAIR) and spin echo (SE) T2-dependent images at baseline showed increased pathologic signaling in both medial thalamic regions (**a**), mammillary bodies (**b**), periaqueductal gray matter (**c**), and wall of the third ventricle (**d**).

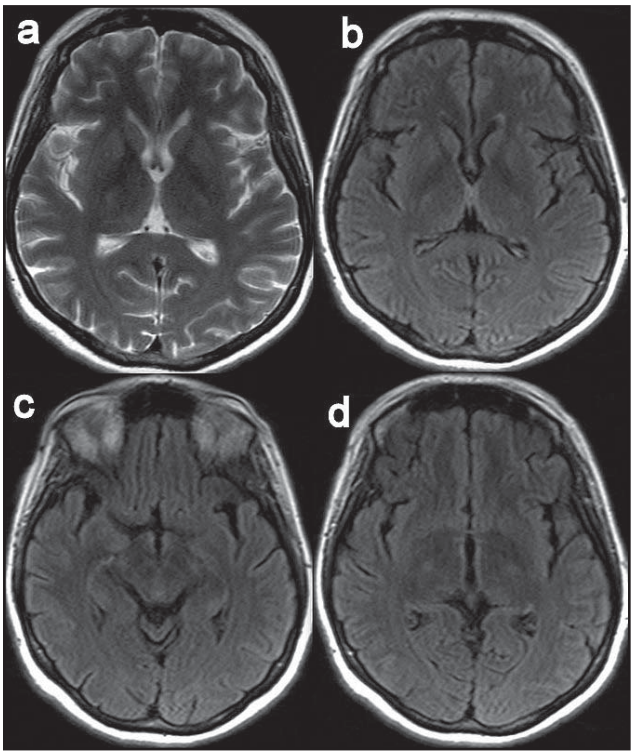

Fig. 3. After 10 days of thiamine treatment, axial FLAIR and SE T2-dependent images showed improvement in pathologic signaling in both medial thalamic regions (**a**), mammillary bodies (**b**), periaqueductal gray substance (**c**), and wall of the third ventricle (**d**).

The human body stores only about 25–30 mg of accumulated thiamine, and these stores are depleted after 2–3 weeks of no thiamine intake (Anonymous 2003). Although thiamine deficiency is almost always alcohol-related in developed countries, it can be secondary to conditions such as hemodialysis, neoplasm, gastric plication surgery, eating disorders, a diet rich in simple carbohydrates, long-term intravenous feeding, severe infections, acquired immunodeficiency syndrome (AIDS), and HG (So & Simon 2004). Thiamine requirements are also increased in conditions that confer high metabolic rates and/or high glucose intake (Wilson *et al.* 2005; Donnino *et al.* 2007), such as pregnancy. The impaired absorption of thiamine may worsen in patients who also have HG (Wilson *et al.* 2005; Donnino *et al.* 2007).

Our patient had been pregnant, had thyrotoxicosis, and had received long-term intravenous glucose and parenteral nutrition without thiamine support. We believe that all of these conditions accelerated the depletion of thiamine in our patient. She also had anemia, hypocalcemia, hyponatremia, hypokalemia, and ketonuria, all of which suggest malnutrition. As a high-metabolism process, thyrotoxicosis only exacerbated the situation, given that thyroid hormones have direct influence on intracellular mitochondrial mass and on carbohydrate metabolism in the Krebs cycle as the main source of energy (Iossa 1991).

To our knowledge, 55 cases of HG-associated Wernicke's encephalopathy have been reported (Chiossi *et al.* 2006; Netravathi *et al.* 2009; Shalchian *et al.*2010; Michel *et al.* 2010; Biotti *et al.* 2011; Yucebilgin *et al.* 2011; Zara *et al.* 2012). In Chiossi and colleagues' report of 49 such cases, there were 16 spontaneous abortions, 2 fetal deaths, and 5 elective abortions resulting from the severity of symptoms (Chiossi *et al.* 2006). The patients were a mean 26.7 years old (range, 18–35 years), and the gestational age averaged 14.3 weeks (range, 4–21 weeks). These women showed neurological signs ranging from drowsiness to coma, in addition to confusion and apathy. Ocular signs, noted in all but two women, consisted of nystagmus, ophthalmoplegia, conjugate-gaze palsy, and amaurosis. In 84% of the patients, cerebellar signs noted included truncal ataxia, dysmetria on finger-to-nose testing, and dysarthria. Hypotonic and depressed tendon reflexes were detected in 22.4% and 57.1% of patients, respectively, and two women had severe neuropathy causing flaccid paraplegia and quadriplegia. Our patient was older but was at a similar gestational stage, and her neurological, neuromuscular, ocular, and laboratory findings were entirely consistent with those reported in the larger group.

Of the six reported patients with thyrotoxicosis complicating Wernicke's encephalopathy (Enoch & Williams 1968; Millson *et al.* 1995; Otsuka *et al.* 1997; Ohmori *et al.* 1999; Bonucchi *et al.* 2008; Wierzbicka-Chimel *et al.* 2011), three have been pregnant (Millson *et al.* 1995; Otsuka *et al.* 1997; Ohmori *et al.* 1999). The first woman was 30 years old and at Week 19 of pregnancy when thyrotoxicosis developed (Millson *et al.* 1995). She received propranolol and propylthiouracil and gave birth to twins at 29 weeks of gestation. Her thyrotoxicosis resolved after delivery, at which time treatment was stopped. The authors did not give an etiology for the thyroid disease. The second woman was 27 years old and at Week 14 of gestation (Otsuka *et al.* 1997). Her thyroid echogram showed increased heterogeneity with diffuse swelling of the gland. She also received propranolol and thiamazole. After her thyroid function had normalized, the echogram revealed diminished size of the gland. She gave birth at 41 weeks, after which time her thyroid dysfunction resolved and the size of the gland remained the same. The authors characterized her disorder as transient gestational thyrotoxicosis arising from circulating HCG. The third woman was 35 years old and at Week 14 of her gestation when she presented with thyroid storm (Ohmori *et al.* 1999). She was given propranolol and propylthiouracil. Her thyroid gland was found to be mildly enlarged with slightly increased blood flow. After receiving 2 weeks of antithyroid medication, she tapered off treatment with no later need for it. Thyrotoxicosis in this case was also attributed to transient gestational thyrotoxicosis. In contrast to all of these cases, our patient had hyperthyroidism resulting from a toxic nodule. Considering her severe HG, we also could conclude that it might have contributed to the clinical picture.

Pregnancy has profound effects on thyroid physiology (Lazarus 2005; Stegnaro-Green *et al.* 2011). Increased excretion of iodine can result in an increase in thyroid volume, and increasing levels of thyroid hormone transport proteins and increased production of T4 and T3 can result in decreased, increased, or unchanged thyroid hormone levels during gestation (Lazarus 2005; Stegnaro-Green *et al.* 2011). HCG secreted from the placenta also can act as a TSH agonist (Lazarus 2005). Pregnancy has an ameliorating effect on autoimmune thyroid disease (Lazarus 2005). The most common cause of autoimmune hyperthyroidism in pregnancy is Graves' disease, occurring in up to 1% of all pregnancies (Patil-Sisodia&Mestman 2010; Krassas *et al.* 2010). Other, less common causes of thyrotoxicosis are toxic multinodular goiter, toxic adenoma, and factitious thyrotoxicosis. The rarest causes are subacute or silent thyroiditis and struma ovarii, hydatiform mole, and TSH receptor (TSHR) mutation activated only during pregnancy (because of hypersensitivity of the mutant TSHR to HCG, only one case of which has been reported) (Lazarus 2005; Stegnaro-Green *et al.* 2011).

We diagnosed HG- and thyroid-associated Wernicke's encephalopathy in our patient based on neurological and mostly radiological findings. Unfortunately, we could not measure thiamine levels quickly for a definitive diagnosis. Measuring thiamine levels can take several days; in the meantime, the initial diagnosis and decisions about treatment can be made based

on clinical grounds (Donnino *et al.* 2007). MRI also plays an important role in diagnosis, given that patients often do not have the classical presentation (Donnino *et al.* 2007; Yucebilgin *et al.* 2011; Bonucchi *et al.* 2008). In Chiossi's review of 49 cases, many had been diagnosed radiologically (Chiossi *et al.* 2006). In one small study, the sensitivity of MRI for detecting Wernicke's encephalopathy was 53%, and the specificity was 93% (Antunez *et al.* 1998). Symmetrically increased signal intensities in the mesencephalic tegmentum, mammillary body, and medial thalamus on proton-density and T2-weighted images are common findings on MRI (Yucebilgin *et al.* 2011). Diffusion-weighted imaging has been found to aid in diagnosis (Bonucchi *et al.* 2008). Because cerebrospinal fluid can mask high-signal lesions on T2-weighted and proton-weighted images, FLAIR sequences might be better in detecting lesions (Ashikaga *et al.* 1997).

Wernicke's encephalopathy should be considered in the differential diagnosis of malnourished patients with altered mental status. High-metabolic states such as hyperemesis gravidarum and thyrotoxicosis can precipitate and worsen this disorder. Treatment should begin promptly, to reduce the likelihood of neurological sequelae and even death.

Disclosure Statement

The authors declare that no competing financial interests exist.

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