CASE REPORT

Wernicke's encephalopathy secondary to gestational hyperthyroidism

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Accepted 10 November 2017

BACKGROUND

Wernicke's encephalopathy is a neurological disorder secondary to the deficiency of vitamin B1 (thiamine). The classic symptoms consist of nystagmus, ophthalmoplegia, ataxia and mental status changes.¹ Initially, this was described by Carl Wernicke in 1881 as acute haemorrhagic polyencephalitis.²

Wernicke's encephalopathy is mostly described in association with malnutrition and alcoholism.¹ However, it has been increasingly being noted in various other settings. There is also evidence that this may be an underdiagnosed condition as several cases may not manifest the classical triad of symptoms. Prompt diagnosis and treatment are essential as any delay or undertreatment can result in irreversible complications.

We report a case of gestational hyperthyroidism causing Wernicke's encephalopathy. To our knowledge, there have been only four previous cases of gestational hyperthyroidism causing Wernicke's encephalopathy in the literature.^{3–7}

CASE PRESENTATION

A 34-year-old G3P2 11-week 6-day-old pregnant female patient presented to the emergency department with a history of confusion, nausea and vomiting. Prior to this, she was admitted a month ago for hyperemesis. At that point, thyroid function tests showed a suppressed thyroid-stimulating hormone (TSH) of 0.01 (0.27–4.2 ng/dL) and high free thyroxine (FT4) of 3.88 (0.9–1.7 ng/dL). Thyroid-stimulating immunoglobulin and thyroid receptor antibody were negative ruling out Graves' disease. She was diagnosed as having gestational hyperthyroidism and treated with hydration and antiemetics, no thionamides were given; her FT4 trended downwards and she was discharged.

Since discharge, she continued to have vomiting, and also developed worsening of her mental status. Although she was prescribed prenatal vitamins, she was unable to take them secondary to persistent vomiting. She had a 30 lb weight loss in the last 1 month. Vitals on admission showed tachycardia of 134 beats/min and a temperature of 98.1. On examination, she was cachectic and had difficulty answering questions. No exophthalmos or thyromegaly was noted. Heart and lung examination was normal except for the tachycardia as described above. Neurological examination revealed a left-sided

nystagmus, equal and reactive pupils, power of 4/5 and decreased reflexes were noted in all extremities. Gait assessment, finger to nose test and Romberg's test could not be performed.

INVESTIGATIONS

Lab assessment (table 1) revealed elevated blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase and bilirubin. TSH was suppressed, FT4 was very high. CT scan of the head done to evaluate mental status changes was unremarkable. Renal ultrasound, done for the evaluation of renal failure, did not show any obstructive pathology. Lumbar puncture did not reveal any infectious pathology, and electroencephalogram showed non-specific cerebral dysfunction. Thiamine levels were checked and were found to be low. MRI of the brain showed T2 hyperintensities and restricted diffusion in the medial thalami, periaqueductal grey matter and dorsal medulla consistent with Wernicke's encephalopathy (figure 1).

TREATMENT

Initially, the patient was admitted to the intensive care unit and started on methimazole 40 mg two times per day. Since the patient was almost at the end of first trimester, methimazole was started instead of propylthiouracil. She also received hydrocortisone 50 mg every 6 hours to guard against relative adrenal insufficiency secondary to hyperthyroidism, propranolol 40 mg every 6 hours to control tachycardia along with aggressive hydration and antiemetics. Once the diagnosis of Wernicke's encephalopathy was made, she was immediately started on high-dose intravenous thiamine replacement and her mental status began to improve. As the FT4 improved and subsequently normalised (table 2), the dose of methimazole was initially decreased to 20 mg two times per day, then 10 mg two times per day and subsequently held. She was discharged to a rehabilitation centre.

OUTCOME AND FOLLOW-UP

On follow-up in the clinic 1 month after discharge, the patient's mental status improved significantly; however, she still had nystagmus and ataxia. She gave birth to a healthy baby boy at 37 weeks weighing 3150 g. After 18 months of extensive rehabilitation, her gait is still very unsteady, and she is a wheelchair user for the most part. She continues

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To cite: Garla VV, Yanes-Cardozo L, Yousuf T, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221644

Table 1 Lab assessment details

Sodium (136–145 mmol/L)	139
Potassium (3.4–4.5 mmol/L)	4.2
Blood urea nitrogen (6–20 mg/dL)	102
Creatinine (0.51–0.95 mg/dL)	2.57
Calcium (8.6–10.2 mg/dL)	11.3
Total bilirubin (0–1 mg/dL)	4.18
Aspartate transaminase (0–32 U/L)	190
Alanine transaminase (0–33 U/L)	614
Free thyroxine (0.93–1.7 ng/dL)	7.7
Thyroid-stimulating hormone (0.27–4.2 ng/dL)	0.01
Thiamine (70–180 nmol/L)	25
Thyroid-stimulating immunoglobulin (≤ 1.3)	1.0
Thyroid receptor antibody (0–1.75 IU/L)	<1

to have bilateral nystagmus; however, her mental faculties have improved and are back to baseline.

DISCUSSION

Wernicke's encephalopathy is secondary to the deficiency of thiamine, a water-soluble vitamin.

Thiamine has a limited storage pool with stores lasting 9–18 days. It is absorbed from the duodenum in a rate-limiting manner. The active metabolite thiamine pyrophosphate is a cofactor in the enzymes involved in carbohydrate and lipid metabolism, production of amino acids and certain neurotransmitters.⁷ Daily recommended allowance of thiamine is 1.4 mg/day or 0.5 mg/1000 kcal. There is an increased demand in conditions such as pregnancy, lactation, critical illness and children. High carbohydrate diet also raises the requirement of thiamine.⁸ Variants of transketolase enzyme that have decreased affinity to thiamine pyrophosphate also may predispose an individual to developing Wernicke's encephalopathy.⁹

Wernicke's encephalopathy is characterised by a triad consisting of mental status changes, gait ataxia and ocular abnormalities. Based on necropsy studies, about 82% patients had mental status changes, which range from mild confusion to acute psychosis, secondary to the changes in the mammillary body and thalamus.¹⁰ About 29% patients had ocular abnormalities (nystagmus, ophthalmoplegia) due to changes in the oculomotor and abducens nuclei. Involvement of the cerebellar vermis causes ataxia in about 23% patients. Of note, 19% patients did not have any of the features.^{11 12}

It is very much an underdiagnosed condition; studies have shown that as many as 80% of the cases are not diagnosed. This is in part due to the fact that very few of the patients, around

Table 2 Thyroid function tests in chronological order

	Previous admission	Previous discharge	Day of admission	3 days	4 days	10 days
Thyroid-stimulating hormone (0.27–4.2 ng/dL)	0.01	0.01	0.01			0.75
Free thyroxine (0.9–1.7 ng/dL)	3.88	2.41	>7.7	2.79	1.32	0.05

16%, have the complete triad of nystagmus, ophthalmoplegia gait disturbances and mental status changes.¹² The possibility of subclinical forms of Wernicke's encephalopathy occurring is also supported by the discrepancy in the prevalence of this condition between pathological and clinical studies.

While Wernicke's encephalopathy has been classically associated with alcoholism and malnutrition, it has increasingly been recognised in association with various other disorders (table 3). Physician needs to be vigilant and have a high index of suspicion for non-classical conditions that can be associated with Wernicke's encephalopathy.¹¹

Wernicke's encephalopathy is a clinical diagnosis that requires a high index of suspicion. Blood levels of thiamine and red blood cell transketolase activity will be low but are not very specific.¹¹ Thiamine or its phosphorylated esters can also be measured in blood by high-performance liquid chromatography.¹³ MRI is 53% sensitive and 93% specific. T2 hyperintensities are seen in the regions of the brain that have a high thiamine turnover (mammillary bodies, thalamus, midline cerebellum, periaqueductal grey matter). However, these lesions are not specific to Wernicke's encephalopathy.¹⁴ EEG may show non-specific slowing.¹¹

No specific guidelines exist on the treatment of Wernicke's encephalopathy. Since the main mechanism of thiamine entry into the central nervous system (CNS) is by passive diffusion, giving large doses of parenteral thiamine replenishes the CNS thiamine level faster. Cook recommended giving thiamine 500 mg intravenous three times a day for 2–3 days and if a response is observed 250 mg intramuscular daily till clinical improvement ceases. It should be borne in mind that undertreatment of Wernicke's encephalopathy leads to irreversible complications.¹⁵

Gestational hyperthyroidism is secondary to the stimulation of the thyroid gland by beta human chorionic gonadotropin. It occurs mostly in the first trimester and can be associated with hyperemesis gravidarum. Treatment consists of restoring volume status, and treatment of nausea. Antithyroid medications are generally not recommended.¹⁶

Table 3 Disorders associated with Wernicke's encephalopathy

1.	Chronic alcohol use
2.	Gastrointestinal disorders (peptic ulcer disease, ulcerative colitis, Crohn's disease)
3.	Surgeries (bariatric surgery, intestinal resection, gastrectomy)
4.	Cancers (colon cancer, gastric carcinoma, non-Hodgkin's lymphoma, large B cell lymphoma, myeloid leukaemia)
5.	Recurrent vomiting or diarrhoea
6.	Medications (erbulazole, ifosfamide, high dose nitroglycerin, tolazamide, chronic diuretic therapy)
7.	Anorexia nervosa
8.	Renal disease
9.	AIDS
10.	Thyrotoxicosis

Figure 1 (A) T2 hyperintensities noted in the periaqueductal grey matter (white arrow). (B) T2 hyperintensities noted in the dorsal medulla (white arrows). (C) T2 hyperintensities noted in the medial thalamus (white arrow).

Hyperthyroidism causes an increase in the demand for ATP and upregulates Krebs cycle. Since thiamine is an important coenzyme in the same, the demand for thiamine increases, this combined with the decreased stores secondary to malnutrition in hyperemesis predisposes to Wernicke's encephalopathy.¹⁷

Hyperthyroidism has been associated with a variety of neuropsychiatric disturbances.^{18,19} Thyroid receptors are concentrated in the limbic system that is responsible for memory. Hyperthyroid patients exhibited grey matter changes primarily in the areas associated with cognitive, emotional and behavioural abnormalities.²⁰ The role of thiamine deficiency in the genesis of neuropsychiatric symptoms associated with hyperthyroidism has not been studied.

In our case, it is likely that the demands of pregnancy combined with reduced intake due to hyperemesis and the hypermetabolic state induced by hyperthyroidism resulted in a rapid depletion of thiamine precipitating Wernicke's encephalopathy.

Learning points

- The classic triad of Wernicke's encephalopathy (mental status changes, gait ataxia and ocular abnormalities) is seen in only 16% patients. Therefore, physicians must not rule out this disorder in patients who may not have one or more of the classic triad components.
- It is being increasingly recognised in association with various conditions (anorexia nervosa, AIDS, postbariatric surgery, inflammatory bowel disease, renal disease and thyrotoxicosis) other than alcoholism.
- Prompt diagnosis is essential as delay in diagnosis leads to irreversible complications.
- MRI with T2 hyperintensities in the mammillary bodies, thalamus, midline cerebellum and periaqueductal grey matter is consistent with the diagnosis of Wernicke's encephalopathy.
- Intravenous thiamine is recommended as treatment to facilitate the entry of thiamine into the central nervous system. It should be borne in mind that undertreatment can also lead to irreversible complications of Wernicke's encephalopathy.

Contributors VVG and LY-C were involved in writing the case description, formatting the images and writing the discussion section. SA and TY were involved in the literature search and editing of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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