Rare disease

Wernicke's encephalopathy induced by hyperemesis gravidarum

Ana Palacios-Marqués, Silvia Delgado-García, Tina Martín-Bayón, Juan Carlos Martínez-Escoriza

Obstetrics and Gynaecology Department, University General Hospital of Alicante, Alicante, Spain

Correspondence to Dr Ana Palacios-Marqués, anapalaciosm@yahoo.es

Summary

Wernicke's encephalopathy (WE) is a reversible neurological emergency caused by thiamine deficiency. Prolonged vomiting in pregnancy results in thiamine depletion. The early recognition of its clinical signs and symptoms is essential to establish the suspected diagnosis and can be confirmed by MRI. Prompt administration of thiamine is important for preventing the occurrence of sequelae in the mother and for improving the fetal prognostic. We report a case of WE induced by hyperemesis gravidarum with a good maternal and fetal outcome.

BACKGROUND

We think Wernicke's encephalopathy (WE) is an uncommon but very severe condition. We believe that it is very important that health providers know it, because if they think about it they can administer a prophylactic treatment and prevent the neurological disorders associated with this disease.

CASE PRESENTATION

A healthy 23-year-old pregnant woman presented at 14 weeks with a 1 month history of weight loss of 20 kg and a 12 h history of discomfort, confusion and drowsiness. She had been treated with intravenous fluids and antianaemic therapy in our hospital for hyperemesis gravidarum without much improvement during the previous 20 days. Initial laboratory tests were remarkable for high liver transaminase levels, but quickly returned to normal values. Her symptoms continued, however, and she was re-admitted for a comprehensive management. She has had one previous successful pregnancy and there was no other significant history in the past. She denied consumption of alcohol or drugs.

On examination she was confused and could not obey simple commands. The pupils were bilaterally equal and reactive. Ocular movements showed no restricted bilateral convergence with horizontal nystagmus. She had preserved muscle tone in all four limbs. The muscle stretch reflexes were ++/+++++ in all four limbs. There were no other neurological deficits. An obstetric abdominal ultrasound showed single live intrauterine gestation of 14 weeks.

INVESTIGATIONS

Laboratory tests showed hypokalaemia over 2.4 mEq/ml, elevated serum liver transaminase levels (aspartate aminotransferase: 363 U/l; alanine aminotransferase: 1143 U/l) and high levels of urinary ketones; other tests showed hypovitaminosis and several hypoalbuminaemia. The other routine urine and some haematological parameters were normal. She was given intravenous lactated Ringer's solution, intravenous metoclopramide and thiamine

therapy. One gastroenterologist consultant said her hypertransaminasemia was explained to be caused by hyperemesis.

The patient's condition and laboratory tests worsened dramatically after 3 h. She was really clouded, with temporal disorientation and no response to simple commands.

An abdomen ultrasound scan showed a minimal hepatic steatosis. There were no traces of drugs found in the urine.

An MRI of the brain revealed symmetrical T2W and FLAIR hyperintensities in bilateral medial thalami. T1-weighted images showed low signal intensity of periaqueductal grey matter and periventricular region of the third ventricle. Diffusion-weighted imaging (DWI) showed increased signal intensities of restricted free water molecule diffusion within medial thalami, splenium of the corpus callosum and hypothalamic (figure 1).

DIFFERENTIAL DIAGNOSIS

Venous sinus thrombosis, pituitary apoplexy, multiple sclerosis, central nervous system tumour, paraneoplastic disease, infections, intoxications, cerebrovascular disease or autoimmune disease.

TREATMENT

She received intravenous thiamine 500 mg three times per day for 2 days and later 900 mg per day, and other vitamin supplements (B complex) and serum albumin during the hospitalisation. Over the next 5 days, there was a gradual clinical and radiological improvement of her encephalopathy.

She received parenteral nutrition from the 5th day and for over 17 days. Afterward she started enteral nutrition by gastrojejunal catheterisation for over 10 days.

OUTCOME AND FOLLOW-UP

The patient was discharged home in good condition after a total hospital stay of 24 days.

At term, a healthy female baby was delivered. The infant, who weighed 2620 g, had Apgar scores of 9 at 1 min and 10 at 5 min. She was discharged with her

Figure 1 Brain MRI. (A, B) Coronal FLAIR images showing symmetric hyperintensity of the medial thalami and mammillary bodies. (C) Axial FLAIR image. Bilateral lesions of thalami are seen with the involvement of the periaqueductal area. (D) Diffusion-weighted images show high signal intensity in these areas. This sequence is helpful in diagnosing Wernicke's encephalopathy.

mother on the second postpartum day. Both the mother and the infant have remained in good health thereafter.

DISCUSSION

WE was first described in 1881 by Carl Wernicke as a triade characterised by confusion, ataxia and ophthalmoplegia and, if untreated, can progress to coma and death.

Thiamine (vitamin B₁) is an essential coenzyme in carbohydrate metabolism. Its deficiency is endemic worldwide. In our setting it is most often observed with alcohol abuse and poor nutrition, but might also be seen in many other conditions (see table 1)^{1 2}; it can also be precipitated by three pregnancy-related conditions: hyperemesis gravidarum, diabetic ketoacidosis and intravenous administration of glucose in the presence of chronically inadequate thiamine intake.³

The daily requirement of thiamine in pregnancy is 1.5 mg, because of the increased demand for thiamine by the fetus and the hypermetabolic state of pregnancy. This is about 36% above the non-pregnant levels.⁴

Body stores of thiamine last for 18 days; hence, prolonged vomiting results in thiamine depletion. In this setting, it is important to emphasise that symptomatic thiamine deficiency may be precipitated by inadequate

thiamine reserves when accompanied by intravenous administration of glucose-containing solutions without vitamins. Also thiamine depletion can be aggravated by other conditions such as hyperthyroidism or gestational thyrotoxicosis.³

Table 1 Conditions associated with increased risk of Wernicke's encephalopathy

Alcoholism
Malignancy
Severe infection
Prolonged vomiting
Hyperemesis gravidarum
Gastrointestinal surgery
Pyloric obstruction
Prolonged parenteral feeding
Residence in a nursing home
Habitually restricted diet in the elderly who live alone
Anorexia nervosa and bulimia
Malnutrition due to child abuse
Haemodialysis or peritoneal dialysis
Fasting and extreme dieting
Hunger strike
Bariatric surgery
Acquired immunodeficiency syndrome

The diagnosis of WE is primarily clinical. Caine *et al*⁵ proposed an operational criterion for the recognition of WE. WE is diagnosed if there exist any two of the following four signs: dietary deficiencies, oculomotor abnormalities, cerebellar dysfunction and/or either an altered mental state or mild memory impairment. In her review of the literature, Di Gangi *et al*⁶ reported that the ocular signs were present in 95.2% of the patients, especially nystagmus; cerebellar signs in 82.5%; ataxia in 74.6%, confusion in 60.3%, hypotonia in 60.3%, memory impairment in 52.3% and severe alteration of consciousness in 30.1% of the cases. According to the Caine criteria, our patient should be diagnosed with this condition when she was admitted because she had three of these criteria: dietary (prolonged vomiting), oculomotor abnormalities (nystagmus) and altered mental state (drowsy and confused). Our patient showed also elevated liver transaminase levels, even during her first admission. It is well known that moderately elevated liver transaminase levels accompany hyperemesis; however, Rotman *et al* suggested that patients with hyperemesis and with elevated liver enzymes are more likely to develop WE than those with normal values.⁷ Although we had the suspicion diagnosis, we did not start the administration of thiamine until we obtained the MRI results.

According to other authors, MRI is particularly important for the initial diagnosis and leads to accurate diagnosis for excluding other conditions such as vascular lesions and thrombophlebitis.⁸ The MRI of the brain has a high specificity (93%) and a moderate sensitivity (53%). Lesions of WE are usually bilateral and symmetric and involve medial thalami, tectum of midbrain and periaqueductal regions along the third and fourth ventricles. It is important to set that the MRI changes in WE have a wide spectrum and may vary with severity and duration of the disease.⁸⁻⁹ Zhong *et al* analysed the serial MRI findings in six non-alcoholic patients with WE and concluded that patients without coma showed only periventricular damage; with further alteration of consciousness there was involvement of the medial thalami and capita of caudate nuclei. WE is remediable when there is involvement of only the periaqueductal regions, medial thalami and caudate; the involvement of the cortical regions suggests irreversible damage and poor prognosis.⁹ We think that it is very important to determine the extent of the injury to establish the long-term maternal prognosis.

Often the diagnosis of WE can be difficult when symptoms are atypical and/or neuroimaging tests show atypical lesions. In these cases, clinical diagnosis is confirmed after therapy with large doses of thiamine.¹⁰

WE is a medical emergency that needs urgent treatment. Parenteral thiamine should be immediately started, which ensures its adequate absorption. Despite recommendations by recent guidelines, nowadays there is no evidence or consensus for the best therapy. Most authors recommend 500 mg per day given four times a day (q.i.d.) for 2 days. If an effective response is observed, 250 mg per day q.i.d. should be continued until the patient tolerates oral thiamine. Doses of thiamine less than 250 mg per day apparently may not be useful. Subsequently, oral thiamine should be continued, although there is no consensus regarding the duration of treatment or the recommended daily dose. The dose ranges from 60 to 100 mg daily for at least 3 months.^{2-6 10-12}

Without treatment the mortality rate ranges from 10% to 20%, but many more victims are left with persistent neurological deficits despite treatment. Complete remission of the disease occurred only in 29% of the cases. Resolution of most of the patients' symptoms required months and permanent impairment was frequently detected.^{2-6 10-13}

The improvement of symptoms started reversing hours to days after the beginning of thiamine administration; the ocular signs improve first followed by ataxia and confusion. In the former review by Di Gangi *et al*⁶, complete resolution occurred within 3 months in 53.9% of the subjects, but in other cases impairment persisted.

Regarding the fetal prognosis, WE is responsible for up to 50% of fetal deaths via direct or indirect mechanisms. Di Gangi *et al*⁶ reported 34.5% spontaneous abortions, 9% elective abortions and 3.6% fetal deaths. Biotti *et al*¹¹ reported a pregnant woman with WE whose fetus suffered from an ischaemic stroke, but there are no specific explanations for the potential increased risk of haemorrhagic or ischaemic fetal stroke. Thiamine deficiency is the cause of intrauterine growth retardation in laboratory rats but the reported birth weight was not reduced; this may be explained by a mild hyperglycaemia that accompanies thiamine deficiency.³⁻¹⁴ Overall, case reports in which thiamine therapy was started within 24 h of the onset of focal neurological deficits have generally had favourable fetal outcomes, as in our case.¹⁵

We agree with other authors in emphasising the importance of prompt thiamine supplementation in pregnant women with prolonged vomiting: oral or intramuscular thiamine supplements (100 mg daily) should be prescribed to pregnant women who present with vomiting and feeding difficulties for more than 3 weeks and intravenous thiamine should be administered, especially before starting intravenous or parenteral nutrition.^{4-14 15} We think that in our case if during her first admission the patient had been given this prophylactic treatment she might not have had the neurological problems.

Learning points

- ▶ Clinical features: confusion, ocular abnormalities and ataxia.
- ▶ Diagnosis: MRI findings.
- ▶ Treatment: intravenous thiamine 100 mg daily.
- ▶ Prophylaxis: oral or intravenous thiamine administration if: there are vomiting and feeding difficulties for more than 3 weeks; or before the administration of carbohydrate solutions in patients with hyperemesis.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Wilson RK, Kuncel RW, Corse AM. Wernicke's encephalopathy: beyond alcoholism. *Nat Clin Pract Neurol* 2006;**2**:54-8.
2. Netravathi M, Sinha S, Taly AB, *et al*. Hyperemesis-gravidarum-induced Wernicke's encephalopathy: serial clinical, electrophysiological and MR imaging observations. *J Neurol Sci* 2009;**284**:214-16.

3. **Selitsky T**, Chandra P, Schiavello H. Wernicke's encephalopathy with hyperemesis and ketoacidosis. *Obstet Gynecol* 2006;**107**:486–90.
4. **Chan-Kyoon Y**, Moo-Hwan Ch, Dong-Cho L. Wernicke-Korsakoff syndrome associated with hyperemesis gravidarum. *Kor J Ophthalmol* 2005;**19**: 239–42.
5. **Caine D**, Halliday GM, Kriel JJ, Harper CG. Operational criteria for the classification of chronic alcoholics: identification of Wernicke's encephalopathy. *J Neurol Neurosurg Psychiatry* 1997;**62**:51–60.
6. **Di Gangi S**, Gizzo S, Patrelli TS, *et al*. Wernicke's encephalopathy complicating hyperemesis gravidarum: from the background to the present. *J Matern Fetal Neonatal Med* 2011;**1**:1–6.
7. **Rotman P**, Hassin D, Mouallem M, *et al*. Wernicke's encephalopathy in hyperemesis gravidarum: association with abnormal liver function. *Israel J Med Sci* 1994;**30**:225–8.
8. **Michel ME**, Alanio E, Bois E, *et al*. Wernicke encephalopathy complicating hyperemesis gravidarum: a case report. *Eur J Obstet Gynecol Reprod Biol* 2010;**149**:118–19.
9. **Zhong C**, Jin L, Fei G. MR imaging of nonalcoholic Wernicke's encephalopathy: a follow-up study. *AJNR Am J Neuroradiol* 2005;**26**:2301–5.
10. **Zara G**, Codemo V, Palmieri A, *et al*. Neurological complications in hyperemesis gravidarum. *Neurol Sci* 2012;**33**:133–5.
11. **Biotti D**, Osseby GV, Durand C, *et al*. Wernicke's encephalopathy due to hyperemesis gravidarum... and fetal stroke: what relationship? *Clin Neurol Neurosurg* 2011;**113**:490–2.
12. **Shalchian S**, de Noordhout AM, Fumal A, *et al*. A rare complication of hyperemesis during pregnancy: Wernicke's encephalopathy. *Acta Neurol Belg* 2010;**110**:209–11.
13. **Chiossi G**, Neri I, Cavazzuti M, *et al*. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. *Obstet Gynecol Surv* 2006;**61**:255–68.
14. **Anoop TM**, Rose L, Sathy MS, *et al*. Hyperemesis gravidarum-induced Wernicke's encephalopathy. *J R Coll Physicians Edinb* 2009;**39**:125–8.
15. **Spruill SC**, Kuller JA. Hyperemesis gravidarum complicated by Wernicke's encephalopathy. *Obstet Gynecol* 2002;**99**:875–77.

This pdf has been created automatically from the final edited text and images.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Palacios-Marqués A, Delgado-García S, Martín-Bayón T, Martínez-Escoriza JC. Wernicke's encephalopathy induced by hyperemesis gravidarum. *BMJ Case Reports* 2012;10.1136/bcr-2012-006216, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow