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*Case Report*

# Wernicke Encephalopathy in a Pregnant Patient with Hyperemesis Gravidarum and Foetal Demise: A Case Report

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## *Abstract*

*Wernicke encephalopathy is a neurologic complication of thiamine deficiency characterised by clinical triad of ophthalmoplegia ataxia and confusion. Wernicke encephalopathy (WE) is an acute problem which requires emergency treatment to prevent morbidity and mortality. This disorder must be differentiated from Korsakoff syndrome which is a chronic neuropsychiatric problem characterised by confabulation and anterograde and retrograde amnesia which occurs consequently to Wernicke's encephalopathy. Hyperemesis gravidarum (HG) has a significant risk for Wernicke encephalopathy especially in the setting of pregnancy. Here we present a case of hyperemesis gravidarum associated Wernicke encephalopathy in a 41-year-old patient who was 16 weeks pregnant, and a delay in arrival to the hospital resulted in foetal demise, severe dyselectrolytemia and symptoms attributing towards WE*

***Case presentation**: We present the case of a 41year-old primigravida African South Indian woman at 16 weeks gestational age who initially presented at a local private hospital with nausea and vomiting that ultimately progressed to severe hyperemesis-gravidarum-associated Wernicke encephalopathy, foetal demise, and hypokalaemia. The patient received a total of two weeks of high-dose parenteral thiamine followed by oral thiamine therapy for another 3 weeks. Neurological clinical evaluation was in accordance with the diagnosis of WE, however MRI brain showed a normal study. Patient responded rapidly to the high dose parenteral thiamine therapy which again strengthened the diagnosis.*

***Conclusions**: In hyperemesis gravidarum thiamine deficiency may cause multi system complications and delay may occur in administering thiamine as the classic symptoms might fail to raise suspicions especially during pregnancy. There is only a low threshold for parenteral thiamine repletion in pregnant women with persistent vomiting as hyperemesis gravidarum-induced severe thiamine deficiency can result in Wernicke encephalopathy, and foetal demise.*

## Introduction

Wernicke encephalopathy (WE) is an acute neurological condition characterized by a clinical triad of symptoms such as oculomotor dysfunction, confusion and ataxia,which is caused due to thiamine deficiency (1). Wernicke encephalopathy (WE) is an acute syndrome which require emergency treatment to prevent neurological morbidity and death. In 1881, Carl Wernicke described an acute encephalopathy characterized by mental confusion, ophthalmoplegia, and gait ataxia and associated it with autopsy findings of punctate haemorrhages around the third and fourth ventricles and the aqueduct. A few years later Russian psychiatrist Sergei Korsakoff described a chronic amnestic syndrome in which memory was impaired far out of proportion than other cognitive domains.

WE is a life-threatening illness caused by thiamine deficiency, which primarily affects the peripheral and central nervous systems. This disorder should be differentiated from Korsakoff syndrome which is preventable and is usually suspected because of at least one episode of Wernicke's encephalopathy. (2),(3) . Around 85% of patients with WE progress to KS without treatment (1). While commonly associated with alcohol use, WE can occur with deficiencies in thiamine intake, absorption, storage, and metabolism from any aetiology and has been associated with bariatric surgery, human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and hyperemesis gravidarum (HG). Thiamine is a cofactor for several enzymes which play a key role in metabolism, including transketolase, alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase (1). The requirements are high during periods of high metabolic demand and high glucose intake. This is manifest by the precipitation of WE in susceptible patients by administration of IV glucose before thiamine supplementation (4). Because of the role of thiamine in cerebral energy utilization, it has been proposed that its deficiency initiates neuronal injury by inhibiting metabolism in brain regions with high metabolic requirements and high thiamine turnover. Events such as blood-brain barrier breakdown, N-methyl-D-aspartic acid (NMDA) receptor-mediated excitotoxicity and increased reactive oxygen species have been implicated in thiamine deficiency-induced neurotoxicity (5). Acute WE lesions are characterised by vascular congestion, microglial proliferation, and petechial haemorrhages. In chronic cases there is demyelination, gliosis, and loss of neuropil with relative preservation of neurons. Neuronal loss is prominent in unmyelinated medial thalamus(1)(6). Atrophy of mamillary body is a specific finding in chronic WE and Korsakoff syndrome. The lesions of WE are distributed in the structure surrounding third ventricle, aqueduct and fourth ventricle.

HG presents a significant risk factor for WE due to persistent vomiting which subsequently causes nutritional deficiency. 80% of all pregnancies are affected by nausea and vomiting, and it becomes the most common indication for hospitalization during the first half of pregnancy. Symptoms become severe in up to 3% of these cases, resulting in weight loss, dehydration, and electrolyte imbalance (2). A recent systematic review of WE in pregnancy revealed a maternal mortality rate of 5% and 48% foetal mortality, in spite of diagnosis and treatment (4). The foetal demise after 20 weeks gestation occurs in about 1 in 175 pregnancies (6). This increased mortality to the foetus is a unique and defining feature of HG-induced WE.

We present a case of HG-associated WE in a patient at16 weeks of pregnancy in which Hyperemesis gravidarum progressed to Wernicke encephalopathy and also led to foetal demise

## Case Report

A 41-year-old primigravida woman at 16 weeks gestation presented obtunded to the hospital for acute-onset altered mental status. She had nausea, vomiting, and poor oral intake noted for past one week and she had multiple visits with emergency department at a local hospital near her house for intractable vomiting and poor oral intake requiring intravenous fluid repletion. Her modified – 24-hour PUQE score (table 1) was16.

Table 1

| QUESTIONS | Score | Score | Score | Score | Score |
|---|---|---|---|---|---|
| In the last 24 hours, for how long have you felt nauseated or sick to your stomach? | Not at all (1) | 1 hour or less (2) | 2-3 hours (3) | 4-6 hours (4) | More than 6 hours (5) |
| In the last 24 hours have you vomited or thrown up? | 7 or more times (5) | 5–6 times (4) | 3–4 times (3) | 1–2 times (2) | I did not throw up (1) |
| In the last 24 hours how many times have you had retching or dry heaves without bringing anything up? | No time (1) | 1–2 times (2) | 3–4 times (3) | 5–6 times (4) | 7 or more times (5) |

Modified PUQE-24, Mild 3-6 points, Moderate 7-12 points, Severe 13-15

She had no past psychiatric history. On examination the patient demonstrated horizontal nystagmus, confusion and ataxia. She was persistently tachycardic to 150 beats per minute and had hypotension. Her lab investigation reports were notable for multiple electrolyte abnormalities, especially hypokalaemia and hypomagnesemia, lactic acidosis, leucocytosis and anaemia (table 2,3). Urinalysis showed protein and ketones (table 4). ECG showed sinus tachycardia and changes pertaining to hypokalaemia such as 'U'waves and inverted T waves. Considering her symptoms and information from her medical history, a provisional diagnosis of hyperemesis gravidarum induced Wernicke encephalopathy was agreed upon.

**Table 2**

| | Normal value | Day 1 | Day 2 | Day 5 | Day 8 |
|---|---|---|---|---|---|
| WCC | 4-10x 1000 | 16 | 12 | 12 | 08 |
| Hb | 11.5-17 g/dl | 8.7 | 9 | 9 | 9.3 |
| RBC | 3.92 – 5.13 million/mm3 | 3.8 | 3.9 | 3.87 | 3.85 |
| Platelets | 150,000 - 400,000/mm3 | 168 | 173 | 193 | 210 |
| RDW | 12% to 15% | 13.3 | 12.7 | 12.9 | 13 |
| MCV | 80 to 100 fL | 90 | 88 | 89 | 92 |
| PT | 12-15 sec | 13 | 13 | 14 | 13 |
| INR | 0.8 – 1.2 | 1 | 1 | 1.1 | 1 |
| aPTT | 22-35 sec | 28 | 29 | 28 | 29 |
| D-DIMER | < 0.5 mcg/L | | 1.3 | | |

**Table 3**

| | Normal value | Day 1 | Day2 | Day 5 | Day 8 |
|---|---|---|---|---|---|
| Glucose | 70-140 mg/dl | 75 | 81 | 99 | 94 |
| Sodium | 135-150 mmol/dl | 133 | 135 | 136 | 140 |
| potassium | 3.5-5 mmol/dl | 2.6 | 3 | 3.3 | 3.8 |
| magnesium | 1.5-2.2 mg/dl | 1 | 1.8 | 1.8 | 1.9 |
| Calcium | 8.2-9.0 mg/dl | 7.7 | 8.2 | | 8.3 |
| bicarbonate | 18-26 mmol/dl | 20 | | | |
| Chloride | 97-109 mmol/dl | 101 | | | |
| BUN | 15-45 mg/dl | 44 | 39 | 36 | 29 |

| | | | | | |
|---|---|---|---|---|---|
| creatinine | 0.8- 1.4 mg% | 1.1 | 0.9 | 0.8 | 0.8 |
| ALT | 2-33U/L | 40 | 38 | 32 | 35 |
| AST | 3-33 U/L | 44 | 45 | 48 | 41 |
| Total protein | 5.7-6.9 g/dl | 5 | 5.3 | 5.3 | 5.9 |
| Albumin | 2.6-4.5 g/dl | 2.3 | 2.5 | 2.3 | 2.8 |
| Alkaline phosphatase | 25-126 U/L | 70 | 67 | 77 | 85 |
| Total bilirubin | 0.1-0.8 mg/dl | 0.8 | 0.7 | 0.6 | 0.7 |

**Table 4**

| | Normal value | DAY1 | DAY 2 | DAY 5 | DAY 8 |
|---|---|---|---|---|---|
| TSH | 0.45-4.5 mIU/ml | 4.3 | | | |
| FT3 | 4.6-9.7 pmol/L | 7.7 | | | |
| FT4 | 12-30 pmol/L | 18 | | | |
| CRP | 0-6 mg/l | 6.3 | 4.7 | | |
| LACTATE | 0.4-2 mmol/L | 2.4 | 1.2 | | |
| URINE ALBUMIN | NIL | ++ | Trace | | |
| URINE ACETONE | NIL | + | nil | | |

Obstetric ultrasound confirmed foetal demise and the obstetric team decided to move forward with medical treatment, since the patient was not fit to undergo a surgical procedure without further optimisation of patient's general condition. An arterial canula was inserted in the left radial artery and 4 lumen central venous catheter was inserted in the right internal jugular vein. She was started on IV Hartmann's fluid (compound sodium lactate) , high dose parenteral thiamine therapy that is 500mg eighth hourly for 2 days and then 250 mg single daily dose for 5 days along with correction of hypokalaemia and hypomagnesemia. IV 5% dextrose normal saline was given after the parenteral administration of thiamine. She was also given a broad-spectrum antibiotics- IV ceftriaxone, antiemetics- ondansetron 4mg 8th hourly and prochlorperazine 12.5mg 8th hourly, and proton pump inhibitors. She was shifted to the intensive care unit for level 2 care. An MRI brain was done, which showed a normal study. Her condition improved gradually

over the next 48 hours, her tachycardia was settled, and blood pressure improved with fluids. The potassium and magnesium were adequately replaced. She was also started on prophylactic dose of low molecular weight heparin. Her blood cultures came back negative, and the antibiotic was stopped after 3 days. After assessment after 2 days, decision was made to shift her to the operation theatre for dilatation and curettage. The procedure period remained uneventful, and she was transferred back to ICU to continue the management for WE. On the 4th day her symptoms had improved significantly. Her tachycardia had settled, and her BP recordings were normal. She had started on small frequent feeds and there was no vomiting. On the 5th day considering her drastic improvement, we decided to shift her to the room from the ICU. Her treatment for parenteral thiamine was continued until the 7th day. Daily lab investigations were done to monitor the complete blood count, electrolytes, renal function and urine routine and ketones. She was discharged from the hospital on the 8th day with 3 weeks of oral thiamine treatment and iron supplements for anaemia.

## Discussion

Even though WE is usually found in patients with chronic alcohol use, this syndrome may be found in any patient with depletion of thiamine due to conditions such as from persistent vomiting as in hyperemesis gravidarum(7)(8), eating disorder(9)(10), HIV AIDS(11)(12)(13), Chronic diarrhoea, bariatric surgery(14)(15), systemic malignancy(16)(17), prolonged parenteral nutrition(18), transplantation(19), hemodialysis(20). In one autopsy study, individuals who did not have history of chronic alcoholism accounted for 23%. WE is diagnosed by a thorough history taking with a focused physical examination, workup and imaging. The clinical diagnosis is established if the patient has two or more of the following symptoms such as ophthalmoplegia, confusion, and gait ataxia along with a history of dietary deficiency of thiamine(21). A complete blood count and comprehensive metabolic panel can be completed to exclude other causes of central nervous abnormality. Unfortunately there are no reliable and accessible measures for thiamine deficiency despite biochemical changes often preceding physical signs. Free thiamine in plasma or serum shows recent intake rather than storage and can be useful in assessing adherence. Tests which reveals the nutritional status such as 24-h urine excretion of thiamine, and specialty blood tests are there but of limited clinical use. Erythrocyte transketolase levels can detect thiamine deficiency(22) . levels of lactate and pyruvate are often measured since thiamine is a cofactor for pyruvate dehydrogenase enzyme. Moreover brain imaging has also limited use, since a normal brain imaging cannot rule out Wernicke encephalopathy

and has got limited use.

Caine et al. criteria was established in 1997 which is now 85% sensitive if patients have two or more of the classic features that include ataxia, confusion and ophthalmoplegia and dietary deficiency. Most of the times the medical history may reveal the risk factors and help in finding the cause of Wernicke encephalopathy, which was once thought to be caused exclusively by chronic alcoholism(23). Modified 24-hour PUQE score is a scoring index for valid assessment to determine the severity of nausea and vomiting(24) . MRI may reveal hyperintense signaling in the periventricular thalamus , mammillary bodies and periaqueductal gray matter. MRI findings are only 53% sensitive but are 93% specific(25). Absence of one or more of the classic symptoms likely leads to underdiagnosis. In one series of study WE was diagnosed premortem in only 26 of 131 patients whose brain revealed chronic WE lesions. All signs of classic symptoms were seen in17 percent, and none were recorded in 19 percent. In this case while the MRI study was normal, since the patient had the classic symptoms and a substantiating medical history of persistent vomiting , a provisional diagnosis of WE was made and appropriate treatment was started. Since the laboratory investigations specific for thiamine was unavailable at our institution we were unable to perform it on admission and was planning to send the samples elsewhere on the next day. However since the patient started responding to the treatment we decided not to send as the results will not change the course of treatment

Hyperemesis gravidarum is a preventable risk factor for non-alcoholic WE in pregnancy and affects 0.3%-2.3% of all pregnancies. In alcoholic patients it generally takes months to years for the WE signs to develop, however the same syndrome may present as early as 6 weeks gestation and progress rapidly in a pregnant woman due to increased thiamine requirement during pregnancy (26). Thiamine requirement increases by as much as 45% for foetal growth and development (27). Blood investigations for free thiamine have shown to be higher in cord blood than in maternal blood, which may suggest that the foetus is able to seclude thiamine at the expense of the mother (28). Importantly, the development of WE during pregnancy has also been associated with a foetal mortality rate as high as 48%

Diagnosis of WE in this patient was made upon the presence of the classical triad considering persistent vomiting during pregnancy and nutritional status of the patient. She presented at 16 weeks gestational age with HG. She went on to demonstrate several characteristics consistent with a diagnosis of WE. It is unclear if the foetal demise was directly caused by her thiamine deficiency, though the vomiting, poor dietary intake and dys-electrolytemia greatly accelerated her course as metabolic demand increased. (29,30,31)

Although the patient presented to the hospital late, almost one week after the onset of vomiting, the rapid

improvement the patient showed could be attributed to the immediate initiation of thiamine supplementation and also the correction of hypokalaemia, hypomagnesemia and adequate volume replacement and this also helped in preventing the progression to Korsakoff syndrome. Royal College of Physicians advocate for thiamine 500 mg intravenously, three times a day for 2 to 3 days. If there is response then to continue the parenteral thiamine 250 mg once daily for 5 days(32). The thiamine needs to be given in combination with other b vitamins. Administration of glucose without thiamine can precipitate or worsen WE. Daily oral administration of 100 mg of thiamine should be continued after the completion of parenteral treatment and after discharge from the hospital until the patients are considered no longer at risk. Magnesium, potassium and other vitamins must also be replaced

## Conclusion

This patient initially presented with the classic symptoms and along with a significant history of persistant nausea and vomiting raised the suspicion of wernicke encephalopathy and therefore we were able to start the parenteral thiamine therapy as soon as possible. The multisystem complications seen in severe thiamine deficiency may sometimes delay timely administration of high-dose thiamine, particularly in pregnancy, in which the classic triad of symptoms may not be sensitive enough due to the rapid progression of neuropsychiatric symptoms in this population. Since in pregnant women with persistent vomiting as HG-induced severe thiamine deficiency, there is a rapid progression to Wernicke encephalopathy and fetal demise. Therefore, we advise to start an early parenteral thiamine therapy for hyperemesis gravidarum patients with at least 2 of the classic triad and a significant history of severe nausea and vomiting with poor nutrition, thereby decreasing the mortality and morbidity of the patient also preventing from progression to Korsakoff syndrome

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