CASE REPORT

Wernicke's encephalopathy secondary to hyperemesis gravidarum: A clinical challenge

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Abstract

Wernicke's encephalopathy (WE) is an acute neurological condition characterized by a triad of ophthalmoplegia, ataxia and altered mental status. The underlying cause is thiamine deficiency, which may be due to multiple aetiologies. Thiamine is essential for carbohydrate and amino acid metabolism. Its deficiency shunts glucose to anaerobic pathways producing metabolic abnormalities. Diagnosing WE relies heavily on clinical suspicion. Magnetic Resonance Imaging can show some specific findings. We report this case of a 35 year old pregnant woman with gestational diabetes who was admitted in hospital for high blood sugar levels and electrolyte abnormalities. She had a history of ten miscarriages. From undergoing laparoscopic cholecystectomy for intractable vomiting to spontaneous expulsion of the foetus to being intubated for acidosis, her hospital stay was prolonged and eventful. Although the cause of her repeated miscarriages could not be established despite extensive workup, thiamine deficiency leading to Wernicke's encephalopathy was the most probable cause.

Keywords: Wernicke's encephalopathy, Thiamine, Lactic acidosis, Metabolic encephalopathy, Hyperemesis gravidarum.

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Introduction

Wernicke's encephalopathy (WE) is a neurological pathology resulting from thiamine deficiency. Its classic triad consists of oculomotor abnormalities, altered mental status and cerebellar symptoms. Caine criteria was proposed in 1997 that aided in diagnosing WE with greater sensitivity.[1] Thiamine is a hydrophilic vitamin that is biologically active in the form of Thiamine Pyrophosphate(TPP) and serves as a cofactor for several enzymes, involved in carbohydrate and amino acid metabolism. Pyruvate Dehydrogenase (converts pyruvate to acetyl-CoA), alpha-ketoglutarate Dehydrogenase (converts alpha ketoglutarate to succinyl-CoA), branched chain alpha-keto acid dehydrogenase (converts branched chain alpha keto-acids to corresponding acyl-CoAs) and trans-ketolase (of Hexose Monophosphate Shunt for the oxidation of glucose) are some important enzymes well-known to require TPP as an essential cofactor for their activity. Because Thiamine is water soluble and is not stored in the body in large amounts, people with restricted intake, excessive requirement, increased metabolism, and losses can become thiamine deficient in a few weeks.[2] Since Thiamine is essential for aerobic glycolysis, its deficiency can produce type B lactic acidosis (Type A lactic acidosis is related to tissue hypoxia).[3] The clinical manifestations of WE result from lesions in specific brain areas such as the cerebellum, midbrain, pons, and vestibular apparatus. At low levels of thiamine, there is impaired glucose oxidation in mitochondria leading to cytotoxic oedema, apoptosis, or necrosis. This results in oxidative stress and upregulation of endothelial nitric oxide synthase producing increased nitric oxide to react with oxygen free radicals and causing cytotoxicity. Krebs cycle is impaired due to the disruption of Pyruvate Dehydrogenase leading to trouble in the synthesis of gamma-aminobutyric acid (GABA) and excess production of lactate, causing focal acidosis. This causes the breakdown of Deoxy Ribonucleic Acid (DNA) and cellular death, which is irreversible. Neuronal death manifests as symptoms of WE. It is considered that WE is an acute condition, which if prolonged or untreated, can lead to the permanent inability to make new memories, along with cognitive and behavioural changes, collectively called Korsakoff syndrome (KS).[4] Only 16% cases of WE present with the typical triad of symptoms. Nearly 80% of the cases may present only with delirium and may get missed during a routine clinical examination.[5] This may also be due to the fact that WE is classically associated with alcoholism, so it is often underdiagnosed in other atypical circumstances.[6]

Case Report

The case of a 35 year old pregnant woman with 19 weeks of gestation is presented who was admitted via emergency department of Shifa International Hospital Islamabad in October 2019. She had recently been diagnosed with gestational diabetes. She presented to us with complaints of intractable vomiting and generalized weakness for three days. There had been a history of nausea and vomiting since the start of her pregnancy, but the frequency had

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Tabele: LLaboratory investigations on admission.

Peripheral Blood	Results	Range	Chemistry	Results	Range
WBC total	9590/µL	4000-1100/ µL	Potassium	2.8mEq/L	3.5-5.1mEq/L
RBC	4.96m/µL	Male 4.5-6.5 m/ µL Female 3.8-5.8m/ µL	Magnesium	1.66mg/dL	1.7-2.2mg/dL
Haemoglobin	15.1g/dL	Male 13-18g/dL Female 11.6-16.5g/dL	Amylase	29U/L	30-110U/L
HCT	41.5%	Male 40-54% Female 38-47%	Lipase	32U/L	10-140U/L
MCV	83.7fL	80-90fL	Blood Ketone	0.5mmol/L	< 0.6mmol/L
MCH	30.4pg	27-32pg	HbA1c	6.1%	Pre-diabetes 5.7-6.4% Diabetes 6.5% or higher
MCHC	36.4g/dL	33-38g/dL	CRP	14.38mg/L	0-5mg/L
Platelet Count	119000/µL	150,000- 400,000 µL			
Neutrophils	76%	54-65%	Venous Blood Gases		
Lymphocytes	16%	25-40%	pH	7.42	7.31-7.41
Monocytes	8%	2-8%	pCO_2	23.1mmHg	41-51mmHg
Eosinophils	0	1-4%	pO_2	30.0mmHg	30-40mmHg
Basophil	0	0-1%	HCO_3	14.9mmol/L	23-29mmol/L

WBC: white blood cells; RBC: red blood cells; HCT: haematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; HbA1c: Glycosylated Haemoglobin A1c; CRP: C-reactive protein; pO_2: partial pressure of oxygen; pCO_2: partial pressure of carbon dioxide.

increased for the past three days with seven to eight episodes of vomiting per day. There was no history of fever, diarrhoea, headache, neck pain, abdominal pain, visual dysfunction, or focal deficit. Initially, she was being managed by a gynaecology team on an outpatient basis for hyperemesis gravidarum with anti-emetics only. She had a daughter, aged seven years, and a history of ten miscarriages, mainly in the second trimester. Workup for antiphospholipid syndrome had never been done previously. In the Emergency Department (ED), she was found to have increased blood glucose levels with normal serum ketones and profound hypokalaemia, so she was admitted in the services of internal medicine. Table shows the investigations done on admission.

At presentation, she had normal vitals with a Glasgow Coma Scale (GCS) of 15/15 and unremarkable systemic examination. She was managed with intravenous anti-emetics, normal saline, infusions of potassium and magnesium for electrolyte replacement, and Regular Insulin according to Sliding Scale. After one day, she developed severe abdominal pain with guarding and tenderness in right upper quadrant (RUQ). Ultrasonography of the abdomen showed gall bladder sludge with a single calculus. Laparoscopic cholecystectomy was performed the next day. Later that evening, the patient became severely short of breath. Her blood glucose was markedly raised and she had severe metabolic acidosis with a pH of 6.8 and bicarbonate levels of 4mmol/L. She was shifted to the medical Intensive Care Unit (ICU) where she was electively intubated for increased work of breathing due to metabolic acidosis. Haematologist was also taken on board so that the workup could be done for Anti-Phospholipid Syndrome (APLS) simultaneously. All baselines and other pertinent investigations were ordered as per ICU protocol. Her serum ketones were found positive and Diabetic Keto Acidosis (DKA) protocol was started. In the ICU, she developed hypotension, was non-responsive to fluids, and had to be started on nor-epinephrine infusion. Cardiogenic shock was ruled out on the basis of normal cardiac enzymes and electrocardiogram. In the meantime, her blood cultures grew Multi Drug Resistant (MDR) Acinetobacter, supporting our suspicion of septic shock. During all this time, her serum lactate was markedly elevated. Liver enzymes were also elevated with a hepatic pattern (congruent with ischaemic liver) and lactic acidosis was attributed to presumed ischaemia (secondary to hypotension). DKA resolved on day three of ICU admission. Cervical cerclage was performed on the same day for open cervical os. Unfortunately, it was followed by spontaneous expulsion of a dead foetus the next day, and dilatation and curettage was done by the gynaecology team. Her ICU stay was further complicated by a deranged International Normalized Ratio (INR) and thrombocytopenia that later evolved into pancytopenia with few schistocytes on peripheral smear. At the same time, there was failure to wean off from artificial support due to low GCS. The Electroencephalogram (EEG) showed moderate encephalopathy. By this time, our differentials included Thrombotic Thrombocytopenic Purpura (TTP) versus Septic Encephalopathy. A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) levels were sent and intravenous methylprednisolone was started in pulse doses, followed by four sessions of plasmapheresis. ADAMTS13 levels were reported normal, thus excluding TTP as a differential. On day 13, a trial of extubation was successful and she was weaned off with a GCS of 9/15. At that time, her neurological examination revealed dis-conjugate eye movements, ophthalmoplegia with bilateral lateral rectus palsy, and the inability to follow simple verbal commands. Urgent Magnetic Resonance Imaging (MRI) was performed, which showed bilateral, symmetrical, non-enhancing T2 and FLAIR high signal abnormalities in thalami (with differentials including acute infarcts vs Wernicke encephalopathy).

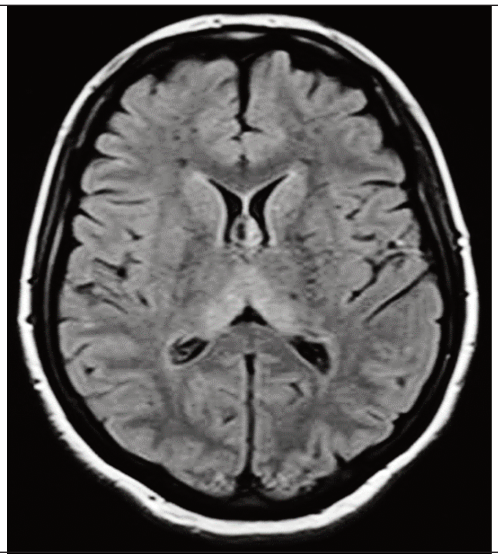

Figure-1: FLAIR sequence showing high signal abnormality in bilateral medial thalami.

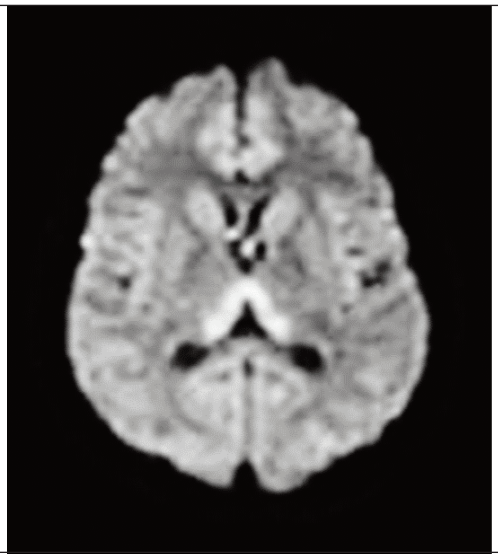

Figure-2: DW1 sequence showing high signal abnormality in bilateral medial thalami.

The same day, she had to be re-intubated as her GCS dropped to 7/15 and she was unable to protect her airway. Considering the recent clinical findings on neurological examination, the history of intractable vomiting, and highly specific findings on MRI, she was labelled as a case of Wernicke's encephalopathy. The Neurology team was already on board. Thiamine levels were not readily available. She was started on high dose intravenous thiamine immediately. Thiamine levels were sent after two days of replacement, which were reported to be just on the lower side of the reference range. This time she was extubated after four days. Her pancytopenia was believed to be secondary to sepsis. All available workup for APLS (Lupus anticoagulant, Anti-cardiolipin antibodies, anti-beta-2 glycoprotein antibodies) were negative. Lactate levels that had peaked at 14.4mmol/L began to decline sharply. Meanwhile, her tracheal culture revealed Multi Drug Resistant (MDR) Acinetobacter and Pseudomonas. Blood culture grew Methicillin-resistant Staphylococcus Aureus (MRSA). Treatment was continued with intravenous antibiotics and thiamine, along with supportive measures, including physiotherapy. Upon stabilization, she was transferred to the medical floor. She was discharged after nearly two months of a prolonged hospital stay with a GCS of 15/15 and improvement in eye muscles coordination.

Discussion

On an average, 0.3-3% of the pregnancies are complicated by hyperemesis gravidarum (HG), the exact pathogenesis of which remains largely elusive. HG has been attributed largely to genetic factors and somewhat to infectious, hormonal and psychiatric aetiologies. Although maternal morbidity is an established consequence, the impact of HG on foetal well-being is still debatable.[7] The prevalence of Wernicke Encephalopathy (WE), as suggested by autopsy studies, is from 0.4% to 2.8%, and on average 1.3%. The classic triad of symptoms is seen in less than one third of the cases.[8] The most commonly observed finding is confusion (82%), followed by eye signs (29%), ataxia (23%) and polyneuropathy (11%).[5] Alcoholism remains to be the most common cause predisposing to WE, but many other causes can be present and must be considered. It is imperative to state that one of the index cases of WE described by Carl Wernicke was a non-alcoholic female who developed pyloric stenosis and thiamine deficiency following ingestion of sulphuric acid.[9] The common aetiologies of WE other than alcoholism include cancer, gastrointestinal surgery, hyperemesis gravidarum, starvation, gastrointestinal tract diseases, AIDS, malnutrition, dialysis and renal disease, parenteral nutrition , vomiting, psychiatric disease, and others.[6] Brain imaging is important in the diagnosis of WE. Long repetition time magnetic resonance imaging (Long TR-MRI) is most useful in detecting the characteristic lesions of WE with 53% sensitivity and 93% specificity. Magnetic Resonance Imaging (MRI) may show typical changes: symmetric alterations in thalami, mammillary bodies, tectal plate and periaqueductal area. Atypical features may also be seen such as symmetric alteration of cerebellum, vermis, cranial nerve nuclei, basal ganglia, splenium or cerebral cortex.[5,10] The diagnosis of WE is based largely on clinical suspicion, and is supported by neuroimaging. Empirical treatment with thiamine leading to clinical improvement confirms the diagnosis. Other diagnostic modalities include the measurement of thiamine levels and an estimation of transketolase activity, which are not readily available. The daily thiamine requirement per day is 1-2 milligrams and may be increased in certain conditions.[11] Without

treatment, WE carries a mortality of 10-15%, although permanent deficits may persist in as many as two-third of the survivors and 25% of the patients may require long term institutionalisation. With treatment, prognosis depends on the severity of the disease and the time of treatment. Ocular signs are the first to improve (within hours) followed by confusion and ataxia.[12] WE in hyperemesis gravidarum is associated with pregnancy loss in nearly half of the cases.[13] Although multiple dosage regimens have been suggested, The European Federation of Neurological Societies suggests a parenteral (intravenous or intramuscular) dose of 200 milligrams of thiamine thrice daily in WE. This should be followed by a normal diet and continued, till symptoms improve. Some British authors recommend a dose of 500 milligrams thrice daily for 2-3 days followed by 250 milligrams daily till improvement of symptoms.[11]

Conclusion

Non-alcoholic Wernicke's encephalopathy is a rare diagnosis. A physician should keep a low clinical threshold for diagnosing this condition. Additionally, thiamine supplementation should be considered in all cases where a patient is nutritionally depleted, as thiamine has a good safety profile and early replenishment can reduce morbidity and mortality.

Ethics: Consent was obtained from all participants in this study.

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Conflict of interest: None.

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