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A rare complication of hyperemesis during pregnancy-Wernicke's encephalopathy

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Abstract : Wernicke's encephalopathy is a potentially reversible yet serious neurological manifestation caused by vitamin B1 (thiamine) deficiency. It is usually suspected in the setting of chronic alcoholism and might not be recognized when associated with other conditions. We describe a young primigravida presenting with hyperemesis gravidarum and altered sensorium. Characteristic brain MRI findings and rapid response to thiamine suggested that she had Wernicke's encephalopathy, possibly due to excessive vomiting and dextrose administration without thiamine supplementation. A high index of suspicion is required, since delayed or lack of treatment may lead to high morbidity and mortality.

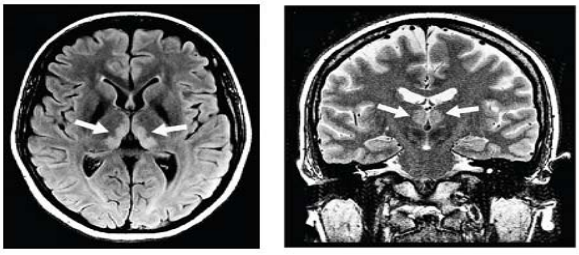
Keyword :hyperemesis gravidarum, Wernicke's encephalopathy, thiamine, Korsakoff psychosis, central pontine myelinolysis

Introduction

Wernicke's encephalopathy is a rare neurological disorder, due to thiamine deficiency and is precipitated by administration of glucose-containing fluids before thiamine supplementation. It was first described by Carl Wernicke in 1881, in patients presenting with the triad of ocular signs, ataxia and confusion, that is seen in 60% of cases [1]. It is typically diagnosed among alcoholics (12.5%), but the prevalence in non-alcoholics varies from 0.04-0.13% in the setting of undernutrition, starvation, prolonged vomiting, anorexia, chemotherapy and total parenteral nutrition [2]. When occurring in hyperemesis gravidarum, it can be fatal in up to 20% of cases, and may even cause spontaneous miscarriage and other fetal complications. Since laboratory tests to confirm the diagnosis are not readily available, almost 80% cases remain undiagnosed; the majority being diagnosed on autopsy [3].We report a case of Wernicke's encephalopathy following hyperemesis gravidarum, with classic clinical and radiographic findings, who showed remarkable response to thiamine replacement.

Case Report

A 25 year old primigravida, at 14 weeks gestation, presented with altered sensorium which was preceded by excessive vomiting for the past few weeks. She gave a history of having been administered 2 pints of dextrose containing fluid at a private clinic the day before admission. Pelvic ultrasound done outside had showed features of missed abortion. On examination, she was restless, confused and had irrelevant speech. Her vitals were stable and hydration was fairly good. Neurologic examination revealed gait ataxia and bilateral horizontal nystagmus. Laboratory investigations including serum electrolytes and urine acetone were unremarkable. Ultrasonography confirmed absence of fetal cardiac activity. A neurophysician consultation was obtained and 300 mg per day of intravenous thiamine started in view of strong clinical suspicion of Wernicke's encephalopathy. Manual vacuum aspiration and check curettage was done under intravenous sedation on day 2 of admission. A brain MRI was subsequently performed which showed spontaneous hyperintensities on FLAIR (a) and T2- weighted images (b) in the medial part of the thalami, with restricted diffusion.



(a) **(b)**

As the clinical signs and MRI findings were consistent with the diagnosis of Wernicke's encephalopathy, intravenous thiamine replacement was continued. Her condition improved gradually over the next few days, and a neurological examination done four days later showed major improvement, except for mild ataxia which resolved over the next month. She was discharged from hospital with significant neurological recovery, with advice to continue oral thiamine 25 mg twice daily for the next three months.

Discussion

Wernicke's encephalopathy is a metabolic disorder due to thiamine deficiency, first described by Carl Wernicke in 1881. He reported a trio of symptoms consisting of drowsiness, ophthalmoplegia and ataxia in three patients (two males with chronic alcoholism and one female with refractory vomiting after sulphuric acid ingestion). On autopsy, he detected punctate haemorrhages affecting the grey matter around the third and fourth ventricles and aqueduct of Sylvius, and designated the term "polio encephalitis hemorrhagica superioris" (4).

Aetiopathogenesis

Although most cases of Wernicke's encephalopathy seen in the western world today are related to chronic alcoholism, it is vital to recognise other rare causes of this condition which account for 0.04% to 0.13% of cases, such as:

-Systemic diseases (malignancy, disseminated tuberculosis, AIDS)
-Starvation (anorexia nervosa, prisoners of war, schizophrenia, terminally ill cancer patients)
-Iatrogenic (refeeding after starvation, chronic haemodialysis)
-Persistent emesis such as hyperemesis gravidarum.

Wernicke's encephalopathy in pregnancy with hyperemesis gravidarum, was first described in 1914 and subsequently, increasing number of cases have been reported [2], with 25 cases published worldwide between 2012-2015 [16]. The mechanism by which thiamine deficiency causes the focal neuropathology lesions found in Wernicke's encephalopathy might be multiple [7]. Thiamine is an important co-enzyme for three critical enzymes in the Kreb's and pentose phosphate cycle: transketolase, ketoglutarate dehydrogenase and pyruvate dehydrogenase complex. Deficiency of thiamine and hence deficiency of these enzymes results in focal lactic acidosis, cerebral energy impairment, depolarization of neurons due to n-methyl-D-aspartate receptor mediated excitotoxicity. Ultimately, it results in alteration of blood brain barrier, generation of free radicals, prompting cell death by necrosis and apoptosis [7].Thiamine is also required to maintain myelin in the brain[7]. The body's 25-30 mg of thiamine storage is derived from diet (unpolished rice, wheat, peas, beans, nuts, etc.) and supplements. This store is depleted before three weeks of deficit, regardless of BMI [16]. It is well understood that thiamine requirements are increased during pregnancy, and even more by the impaired absorption due to hyperemesis gravidarum[8].

In addition, sequestration of the vitamin by the fetus and placenta [9] can reduce blood levels of thiamine even more. Therefore, the recommended thiamine intake of 1.4-1.5 mg per day during pregnancy is inadequate for pregnancies with multiple gestations or hyperemesis [19]. Intravenous dextrose administered before correction of thiamine, in conditions of reduced intake, will aggravate matters further. Other predisposing factors for thiamine deficiency include inadequate intake, refeeding/parenteral nutrition, malnutrition, hypomagnesemia, hypoproteinemia, malabsorption, cachexia, multiple gestation, and anemia [16].

Clinical manifestations

In 1997, Caine et al. proposed an operational criterion for the diagnosis of Wernicke's encephalopathy according to which the condition is recognized if there are two of the following four signs:

(i) dietary deficiencies
(ii) oculomotor abnormalities
(iii) cerebellar dysfunction, and
(iv) either an altered mental state or mild memory impairment [5].

However 10-47% of patients lack these classical signs and instead, manifest with non-specific symptoms such as headache, nausea, anorexia, irritability and abdominal discomfort, before progressing to spastic paresis and myoclonus with nuchal rigidity [16]. Additional signs that may be seen include weakness, dysarthria, akinetic mutism, aphasia, cardiac failure and seizures [16].Mental status changes are nearly universal and exhibited as dizziness, drowsiness, apathy, and cognitive impairment [18]. Gait abnormalities range from weakness to inability to stand [18], and may be somewhat difficult to identify in hyperemesis patients experiencing vertigo and postural hypotension.

Investigations

Confirmatory laboratory testing of thiamine levels may be confusing, as current testing reflects only 0.8%-10% of the body's thiamine stores and represents recent thiamine intake [16].Further, thiamine testing is not always available or reliable, and researchers report that upto 50% of Wernicke's encephalopathy patients have normal thiamine levels [16]. Laboratory assessment of blood transketolase activity and thiamine pyrophosphate (TPP) are also not reliable. MRI is the imaging modality of choice because it is highly specific (93%) and comparatively safer than computed tomography (CT) scan. MRI of the brain shows symmetrically increased signal intensity in the mamillary bodies, dorsomedial thalami, tectal plate, periaqueductal area and around the third ventricle on FLAIR and T2 weighted images.

Treatment

Clinical and experimental data indicate that orally administered thiamine hydrochloride is ineffective in increasing blood thiamine levels or improving symptoms of encephalopathy[10]. Guidelines by the European Federation of Neurological Societies (EFNS) recommend that thiamine should be given 200 mg thrice daily via intravenous route, started before any carbohydrate, and continued until there is no further improvement in signs and symptoms [10]. In nonalcoholic patients, an intravenous dose of thiamine 100-200 mg once daily could be enough; whereas in alcoholic patients, higher doses may be required [11]. Symptom resolution starts within six hours of thiamine replacement [22]. If thiamine administration is commenced immediately, along with parenteral nutrition, feto-maternal morbidity and mortality are prevented; the longer the delay, the poorer the outcome.

Failure to treat Wernicke's encephalopathy

Wernicke's encephalopathy is a medical emergency. Untreated, it leads to death in up to 20% of cases (12), or, in 85% of the survivors, it progresses to the chronic form of the condition, the Korsakoff syndrome due to interruption of diencephalic-hippocampal circuits involving the thalamic nuclei and the mammillary bodies (13). Around 25% of the Korsakoff group will require longterm hospitalization(14). Clinically, Korsakoff psychosis is characterized by a memory disorder occurring in clear consciousness.These patients show a severe impairment of current and recent memory, repeatedly asking the same questions over and over again, and failing to recognize people they had met since the onset of the illness. The illness seems to affect mainly the consolidation of recent memory traces more than remote memories, but the impairment may involve memories from up to 30 years before. Sometimes, affected individuals fill the memory gaps creating "false memories" (confabulations). Such patients are found to benefit from high doses of intravenous corticosteroids in addition to thiamine replacement [17].

Other neurological complications in hyperemesis

Hyperemesis can further be complicated by life threatening conditions like central pontine myelinolysis and extra-pontine myelinolysis which are rare osmotic demyelination syndromes that occur with rapid overcorrection of hyponatremia [6]. These syndromes are induced by slight increases in osmotic pressure attributable to electrolyte infusions, especially in the presence of severe infections, cachexia, and electrolyte imbalances. They are characterized pathologically by

non-inflammatory demyelination of various brain structures resulting in confusion, pseudobulbar palsy, dysarthria, dysphagia, spastic paresis, cognitive deficits, seizures, tremor, myoclonus, and dystonia [15]. Common predisposing factors are alcoholism, malnutrition, liver disease, hyperemesis gravidarum, hyponatremia and hypophosphatemia [18].

Fetal complications

Thiamine deficiency in itself adversely impacts the fetus, increasing the risk of spontaneous abortion, cranial malformations, impaired brain development, neuromotor immaturity, low birth weight, and IUGR [16]. Birth of a normal live baby has been reported in 50% pregnancies complicated by Wernicke's encephalopathy[16]. The fetal loss rate is 33% if Wernicke's encephalopathy and osmotic demyelination syndrome occur concurrently in hyperemesis gravidarum [16]. In addition, 85.2% of babies born to thiamine deficient mothers develop thiamine deficiency within 3-4 weeks of breast feeding and have a greater incidence of SIDS, behavioural changes, autism, delayed language development, and decreased visual alertness [20]. Hence addressing thiamine deficiency proactively during pregnancy not only benefits mothers, but also their infants.

Prevention of thiamine deficiency

The EFNS recommends prophylactic parenteral administration of 200 mg of thiamine, before carbohydrates are started, in all women with hyperemesis presenting with neurological symptoms or suspected to be at risk for Wernicke's encephalopathy[10]. Besides this, a few other practice recommendations to be considered for the prevention of thiamine deficiency were laid out by MacGibbon et al [16].Pregnant women with nausea and vomiting and those carrying multiple fetuses may be prescribed prenatal vitamins containing a minimum of 5 mg of thiamine[16]. Women with a personal or family history of hyperemesis may be prescribed preconceptional oral supplements containing critical nutrients like thiamine and pyridoxine to correct deficiencies[16]. In asymptomatic patients, parenteral thiamine may be substituted with oral forms, preferably with a thiamine derivative such as thiamine tetrahydrofurfuryl disulfide, which is more readily absorbed than thiamine hydrochloride. Given its short half-life, thiamine should be taken at least twice daily for three months or more in 30-50 mg doses [21]. Our patient had a significant history of severe vomiting during pregnancy, with poor intake and intravenous dextrose supplementation which led to Wernicke's encephalopathy. She presented with acute mental confusion, ataxia and opthalmoplegia. MRI of the brain was diagnostic and treatment was started without any delay to which she responded remarkably. Further progression of the disease to Korsakoff's psychosis and osmotic demyelination syndromes was also halted. Miscarriage indirectly improved her nutritional status and thiamine absorption.

Conclusion

Wernicke's encephalopathy should be considered in the differential diagnosis of pregnant patients with persistent vomiting and neurological alterations as, if left untreated, it may lead to severe irreversible and persistent neurological sequela or death. We would like to emphasize the importance of prompt thiamine supplementation in pregnant women with prolonged vomiting in pregnancy, especially before starting intravenous or parenteral nutrition.

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