Wernicke's Encephalopathy Following Hyperemesis Gravidarum

A Report of Three Cases

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SUMMARY – *Wernicke's encephalopathy (WE) due to causes other than chronic alcohol abuse is an uncommon and often misdiagnosed condition. In the setting of hyperemesis gravidarum, an acute deficiency of thiamine results from body stores being unable to meet increased metabolic demands. The condition produces typical clinical and radiological findings and when diagnosed early and treated promptly has a good prognosis. Magnetic resonance imaging (MRI) is sensitive and specific for diagnosis. We describe three patients with hyperemesis gravidarum who developed WE, and highlight a range of clinical and imaging features important for appropriate diagnosis. A high degree of clinical suspicion is essential. Treatment is often empirical pending results of investigation, and consists of parenteral repletion of thiamine stores. Reversal of MRI findings parallels clinical improvement. Neurologic outcomes are usually good, but half the pregnancies complicated by this condition do not produce healthy children.*

Introduction

First described by Carl Wernicke in 1881 as *polioencephalitis hemorrhagica superioris* with a clinical triad of ataxia, confusion and ophthalmoplegia and elaborated as *polyneuritic psychosis* by Korsakoff in 1887, Wernicke's encephalopathy (WE) is a common but frequently missed condition^{1,2}. It occurs due to acute or chronic deficiency of thiamine, the first vitamin in the B series. This disorder may be associated with alcoholism, prolonged starvation, hyperemesis gravidarum, malnutrition, malignant disorders, gastrointestinal disorders, chronic kidney disease or dialysis, thyrotoxicosis, anorexia nervosa, pyloric stenosis, organ transplantation, or total parenteral nutrition¹⁻³. Diagnosing the acute form of WE is very important as it is potentially treatable and the patient may have a complete neurological recovery. Although there are an increasing number of cases being reported in literature, WE following hyperemesis of pregnancy is still a frequently underdiagnosed condition and is often confused with other diseases like acute disseminated en-

cephalomyelitis, pituitary apoplexy, deep cerebral vein thrombosis and neuroinfection³. We describe a series of patients who presented with altered consciousness following prolonged hyperemesis gravidarum and were subsequently diagnosed to have WE.

Case Series

Clinical and imaging details are provided in Table 1. Three women, two of whom were primigravidae, presented in the late first trimester with vomiting beginning four to ten weeks previously. This occurred up to nine times daily, and was not controlled with oral medication. One patient had had hyperemesis in her previous pregnancy which had ended in a spontaneous abortion nine months previously, but no patient reported prior neurological illness.

Neurological symptoms began one to 15 days before admission. All patients had altered consciousness with dysarthria, nystagmus, quadriparesis, and ataxia but ophthalmoplegia was seen in only one patient. One patient had ex-

Table 1 Clinical and imaging features, and outcomes after treatment.

Patient	1	2	3
<i>Antecedent Factors</i>			
Age (years)	26	24	27
Gravida	1	1	3
Onset of vomiting (weeks of gestation)	12	11	5
Duration of vomiting before presentation (weeks)	5	4	10
Alcohol consumption	No	No	No
Signs of malnutrition	Pale, stomatitis, cheilitis	Underweight, stomatitis	Underweight
<i>Neurological features</i>			
Onset of neurological symptoms (days before presentation)	4	1	15
Cognitive impairment	Drowsy but arousable, disoriented, impaired attention and recent memory	Alert but irritable and mildly disoriented, with impaired recent memory	Restless, but cognitively normal
Dysarthria	Bulbar dysarthria	Bulbar dysarthria	Yes
Oculomotor palsies	None	Bilateral lateral rectus weakness	None
Nystagmus	Horizontal + rotatory nystagmus in primary position and on lateral gaze bilaterally	Gaze evoked horizontal + vertical nystagmus	Gaze evoked torsional + horizontal nystagmus
Appendicular ataxia	Bilateral	Marked	Yes
Gait ataxia	Yes	Marked	Yes
Reflexes	Absent	Absent in lower limbs	Brisk in lower limbs
Corticospinal signs	Extensor plantar responses	None	Brisk reflexes in lower limbs
<i>Systemic features</i>			
Hemoglobin	7	12	11
Liver dysfunction	Hyperbilirubinaemia (3.2 mg/dL)	Elevated liver enzymes	No
Other	Metabolic acidosis, thyrotoxicosis	No	Pregnancy-related thyroid dysfunction
<i>MRI findings</i>			
Areas involved	Mammillary bodies, medial thalami periaqueductal grey, tectal plate, dorsal pons and medulla	Medial thalami, tectum, inferior colliculi	Medial thalami, hypothalamus, tectum
T2, FLAIR	Hyperintense	Hyperintense	Hyperintense
DWI	Restricted	Restricted	Restricted
<i>Treatment and Outcome</i>			
Therapy	Intravenous thiamine 500 mg/d for 3 days, then oral	Intravenous thiamine 800 mg/d for 7 days, then oral	Intravenous thiamine 800 mg/d for 7 days, then oral
Time to clinical improvement	15 days	10 days	15 days
Residual deficits at discharge	Dysarthria, dysphagia, nystagmus	Mild ataxia, dysarthria	Mild ataxia, nystagmus
Follow-up available (weeks), persistent deficits	25, no deficits	No follow-up	35, mild gait ataxia and dystonia of hands
Delayed complications	None	Not known	Depressive disorder
Pregnancy outcome	Healthy boy delivered vaginally at term	Intrauterine death at 17 weeks	Intrauterine death at 20 weeks

trapyramidal involvement, with bilateral limb rigidity and dystonia of both hands. Corticospinal signs were present in two patients. One patient had hyperbilirubinaemia, thyrotoxicosis

and anaemia, and another had low thyroid-stimulating hormone levels with normal thyroxine and triiodothyronine, suggesting pregnancy-related thyroid dysfunction.

Figure 1 MRI of patient 1 showing hyperintense lesions in the medial thalami, tectum and dorsal medulla on T2-weighted images (A) and FLAIR images in axial (B) and sagittal (C) planes. Diffusion-weighted imaging (D) shows restricted diffusion with hypointensity on ADC maps. One month after treatment, axial and sagittal FLAIR images (E) were normal.

Figure 2 MRI of patient 2 showing hyperintense lesions in the medial thalami on axial T2-weighted (A) and FLAIR images (B). Diffusion-weighted imaging (C) shows restricted diffusion.

Multiplanar multiecho unenhanced MRI of the brain was performed on a 1.5 T Siemens Avanto MR system using a standard head matrix. Involved areas included the medial tha-

lami, tectum, mamillary bodies, hypothalamus, dorsal pons and medulla. Reversal of signal changes after treatment was demonstrated in one patient (Figure 1).

Figure 3 MRI of patient 3 showing hyperintense lesions in the medial thalami and tectum on coronal FLAIR (A) and axial T2-weighted (B). Diffusion-weighted imaging (C) shows restricted diffusion.

All three patients were treated with high-dose parenteral thiamine, and showed considerable clinical improvement within two weeks. Ataxia and altered consciousness improved first, with a later reduction in dysarthria and nystagmus. One patient (with extrapyramidal features) developed major depression with attempted self-harm two months after discharge and was treated with venlafaxine and alprazolam. Only one patient had a successful outcome to her pregnancy.

Discussion

Thiamine (vitamin B1) is an essential water-soluble vitamin and the body stores about 25-30 mg, which last for about 18 days. The recommended daily allowance (RDA) is 0.4 mg / 1000 kcal, easily met by an average adult diet⁴. However, in pregnancy the requirement of thiamine may increase up to 1.5 mg/day⁵. Wernicke's encephalopathy (WE) occurs due to thiamine deficiency but the exact biochemical mechanism remains unclear.

Thiamine pyrophosphate is predominantly found in the brain and is an important cofactor for enzymes involved in the pentose phosphate pathway^{1,3}. Deficiency of thiamine thus affects energy metabolism, more profoundly in tissues with high thiamine turnover such as neural parenchyma ultimately resulting in cell death from necrosis or apoptosis^{2,3}.

WE of pregnancy has been attributed to poor nutritional intake, increased demands of pregnancy and depleted thiamine stores¹. Hyperemesis leads to lowered thiamine levels³. All our patients were underweight and appeared malnourished. However, individual differences in genetic susceptibility mean that WE following hyperemesis gravidarum is uncommon even though hyperemesis of pregnancy is rather common⁶. WE following hyperemesis gravidarum usually occurs at 14 - 16 weeks of gestation, following more than three weeks of vomiting¹.

More than 50% of patients with hyperemesis gravidarum and WE show liver function abnormalities, probably due to a nutritional cause. In addition, hyperemesis gravidarum with liver dysfunction has an increased risk of WE⁷. Two of our three patients had biochemical evidence of liver dysfunction, and all had excessive vomiting for more than a month before admission.

Two of our three patients had thyroid dysfunction, probably contributing to WE. Gestational thyrotoxicosis, occurring due to the action of human chorionic gonadotropin which is partly homologous to thyroid stimulating hormone, was found to be related to hyperemesis-induced WE which is postulated to be due to reduced intake and absorption of thiamine and its increased utilization^{8,9}.

Classically, patients with WE usually present with a triad of encephalopathy, ataxia and oculomotor symptoms (nystagmus and gaze palsies being the most common), but this syndrome is

not always seen, as in our patients. In pathologically proven cases of WE (n=131), as many as 18.6% had none of the signs of the clinical triad, while 37.1% had one and 27.8% had two signs¹⁰. Encephalopathy usually presents as a state of global confusion, lethargy, and sometimes agitation. Vestibular dysfunction is a common finding. Most adults also have associated features of peripheral neuropathy such as absent deep tendon reflexes, hypotonia and weakness of the lower limbs⁷.

A large number of patients have associated antegrade and retrograde amnesia, so-called Korsakoff's psychosis. None of our patients had memory deficits at discharge, but one developed an affective disorder which needed antidepressant treatment. The association of this mood disorder with extrapyramidal involvement in this patient is interesting given the role of the basal ganglia in cognition.

Upper motor neuron and pontine involvement (evidenced by extensor plantars, hyperreflexia, gaze palsies, spastic quadriparesis, spastic dysarthria or bifacial weakness) in WE suggests concomitant central pontine myelinolysis probably due to the susceptibility of myelin to thiamine deficiency. However, bulbar palsy and pyramidal signs are not usually seen in WE¹¹. One of our patients had bulbar palsy, probably due to bilateral medullary lesions on her MRI, which is a rare finding². Although clinical evidence of corticospinal involvement was seen in two patients, no imaging features of osmotic demyelination were seen.

Caine et al. proposed new operational criteria for the diagnosis of WE alone or in combination with Korsakoff's psychosis or hepatic encephalopathy which required the presence of two of four signs (dietary deficiency, oculomotor abnormalities, cerebellar dysfunction and either an altered mental state or mild memory impairment)¹².

A high index of suspicion is needed for diagnosis of WE following hyperemesis gravidarum which is usually based on clinical features, reversal on treatment with thiamine, MRI findings and activity of transketolase enzyme. Blood pyruvate and lactate levels may also indicate thiamine deficiency. However, transketolase estimation is a complex, expensive assay and is not readily available³. We were unable to measure transketolase activity as the assay is not available locally. In addition, the correlation between transketolase activity and severity of the thiamine deficit is not exact¹³ and treatment should not wait for assay results⁸. Moreover, as treatment with thiamine does not have any known

side-effects, empirical treatment with thiamine in the form of multivitamins is usually the norm.

MR imaging features in combination with clinical signs are most useful for the diagnosis of WE¹. Antunez et al. reported a sensitivity of 53% and specificity of 93% for MRI in the diagnosis of this condition¹⁴. MRI changes are widespread and vary with severity and duration. T2-hyperintensity may be seen in the medial thalami, in the peri-aqueductal gray matter and adjacent to the third and fourth ventricles^{1,15}. Rarely, lesions are found in the caudate nucleus, medulla, hypothalamus or only in the mammillary bodies. These sites are sensitive to thiamine deficiency as they depend on oxidative phosphorylation. One of our patients showed extensive signal changes, from the thalami to the dorsal medulla, while the others had more restricted involvement. Diffusion-weighted imaging (DWI) reveals diffusion restriction and has been recommended to enhance the sensitivity of MRI in making a diagnosis^{16,17}. The signal change corresponds to spongy degeneration of neuropil^{2,18}. Restricted diffusion may be due to a breakdown of cell membranes as thiamine plays an important role in maintaining osmotic balance across cell membranes. Another hypothesis involves a form of vasculopathy^{16,17}.

There is usually not much difference between alcoholic and non-alcoholic WE but long-standing thiamine deficiency as occurs more often in alcoholics may show associated vermian atrophy and contrast enhancement of the mammillary bodies³ which is due to blood-brain barrier disruption and a feature of long-term thiamine deficiency^{19,20}. These patients may have associated anterior corpus callosum atrophy whereas splenial atrophy is seen with non-alcoholic WE²¹.

The neurological features of WE follow the abnormalities in specific regions of the brain. The thalamomesencephalic abnormality is said to be the cause of a disturbance in the level of consciousness, while ophthalmoplegia and ataxia probably correspond to the hyperintensity seen in the tectum, mesencephalic tegmentum, cerebellum and the pons². Patients without coma show only periventricular changes while unconscious patients may show involvement of the caudate head and medial thalami. T2 and FLAIR hyperintensities have also been reported in patients developing deep coma and these probably suggest a poorer prognosis^{19,22}. Patients who develop Korsakoff's psychosis have extensive diencephalic lesions².

Follow-up MRI usually shows a reduction or disappearance of the lesions², as was seen in

one of our patients. Studies on patients with hyperemesis gravidarum have reported that six to 18 weeks after treatment, the size and intensity of the lesions had reduced and the scan was normal four weeks after delivery^{1,13}.

Any patient with hyperemesis gravidarum or prolonged vomiting of any other cause should receive thiamine supplements^{1,2}. Various authors have recommended doses ranging from 50 mg/day up to 200-1200 mg/day parenterally for two weeks followed by oral thiamine of 60 mg/day till the end of the pregnancy^{1,4,11}. Magnesium sulphate given IV 1-2 ml of 50% solution is also recommended along with thiamine as magnesium is a cofactor for transketolase². Hydrocortisone may be given for associated thyrotoxicosis, as it inhibits peripheral conversion of thyroxine to the more active triiodothyronine⁸.

The prognosis of patients with WE following hyperemesis gravidarum is generally good if detected and treated early. Clinical improvement may be seen within six hours in some cases. Oc-

ular symptoms improve faster than confusion, which resolves earlier than ataxia. Language deficits and ataxia take more than a week to improve¹³. Deep tendon reflexes may recover a month after treatment⁸. Mild ataxia, dysmetria and nystagmus may persist, as seen in our patients^{2,3,7}. The outcome of pregnancy in patients with WE, on the other hand, is not very good. In one study, only half the cases resulted in normal children¹. Two of our patients had a poor outcome, with death of the fetus. Togay-Isikay et al. reported that ten out of 29 patients had healthy babies while two had severe neurologic sequelae and three patients died⁷.

In conclusion, WE arising from hyperemesis gravidarum is an uncommon and often misdiagnosed condition. A high index of suspicion facilitates early and accurate diagnosis, prompt treatment and can prevent morbidity and possibly improve pregnancy outcomes. MRI plays an important role in diagnosis, but often empirical treatment with thiamine must be resorted to.

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