Wernicke's encephalopathy: a preventable cause of maternal death

Wernicke's encephalopathy is a rare cause of maternal death. It is a difficult diagnosis to make but prevention and treatment is straightforward. Severe thiamine deficiency causes Wernicke–Korsakoff syndrome. Correct diagnosis and treatment with thiamine will decrease the case fatality rate.

Wernicke's encephalopathy caused by vitamin B1 (thiamine) deficiency is characterized by ophthalmoplegia, ataxia, confusion and confabulation. The typical ocular signs are abducens (VI) nerve palsy, gaze palsy or nystagmus (Nelson-Piercy, 2006).

Wernicke's encephalopathy is found in patients with hyperemesis gravidarum, alcohol-dependent patients who are consuming virtually no food at all, patients with anorexia nervosa and in people whose only food consumed is polished rice (Elia, 2005). Other causes are malabsorption, bariatric surgery, schizophrenia, refeeding after starvation, intravenous hyperalimentation, chronic haemodialysis (Xiong and Daubert, 2009) and possibly iatrogenic diuresis (*Table 1*). The disease may be precipitated by intravenous fluids containing dextrose.

There were three deaths in the Confidential Enquiry into Maternal Deaths in the United Kingdom between 1991 and 1993 which were probably the result of Wernicke's encephalopathy (Department of Health, 1996). Inappropriate management of severe vomiting in pregnancy can be associated with maternal morbidity and mortality related to thiamine deficiency (Nelson-Piercy, 2006).

Table 1. Causes of Wernicke–Korsakoff syndrome

Persistent emesis	Hyperemesis gravidarum
	Bariatric surgery
	Intestinal obstruction
Starvation	Anorexia nervosa
	Schizophrenia
	Prisoners of war
Iatrogenic	Intravenous hyperalimentation
	Chronic haemodialysis
	Iatrogenic diuresis
Uraemia	
Chronic alcohol abuse	
Nutritional deficiency	

Pathophysiology

The active form of thiamine, thiamine pyrophosphate, is an essential cofactor in carbohydrate metabolism and hexose monophosphate shunt (Elia, 2006). In carbohydrate metabolism, thiamine pyrophosphate is necessary in the oxidative decarboxylation of acetyl CoA in mitochondria. Thiamine pyrophosphate facilitates the conversion of pyruvate into acetyl CoA by pyruvate dehydrogenase enzyme complex. In the Krebs cycle, thiamine pyrophosphate is the key enzyme for the decarboxylation of alpha-ketoglutarate to succinyl CoA. In hexose monophosphate shunt, thiamine pyrophosphate is the cofactor for transketolase.

Thiamine deficiency impairs pyruvate dehydrogenase with accumulation of lactate and pyruvate causing vasodilatation and oedema, but the precise mechanism by which it causes Wernicke's encephalopathy is not clear. As a consequence of the body's inability to metabolize carbohydrate to produce energy (adenosine triphosphate), it increases the production of ketone bodies as a compensatory mechanism. The brain and the heart depend on ketone bodies for their energy needs in these circumstances.

There are symmetrical lesions found in the peri-acqueductal and para-fourth ventricular grey matter with or without cerebellar involvement on magnetic resonance imaging. The vestibular apparatus is also affected. The amnestic component (Korsakoff psychosis) is thought to be related to damage in the medial thalamus and diencephalic connections with the medial temporal lobes and amygdala.

Thiamine is found in many natural foodstuffs such as cereals, grains, beans, nuts, pork and duck. Flour and breakfast cereal are usually fortified with thiamine. Thiamine is water soluble and is absorbed from the duodenum. Following absorption, it is found in all tissues,

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but mainly in the liver. The body has approximately 18 days' worth of thiamine stores. Therefore, signs of deficiency quickly develop with poor intake and/or absorption. The recommended dietary requirement of thiamine should be increased if the diet is high in carbohydrate or metabolism and/or excretion is higher. These emphasize the importance of thiamine in pregnancy.

Clinical features

Wernicke's encephalopathy is used to describe the triad of confusion, ataxia and nystagmus (*Table 2*). However, a review of 49 patients with hyperemesis (Chiossi et al, 2006) reported the classical triad of symptoms in 47%, while ocular signs were seen in 96% and ataxia affected about 82% of patients. When memory and learning deficits are also present, it is called Wernicke–Korsakoff syndrome.

Table 2. Neurological signs

Eye signs	Nystagmus
	Bilateral lateral rectus palsies
	Conjugate gaze palsies
	Fixed pupils
	Rarely, papilloedema
Ataxia	Broad-based gait
	Cerebellar signs
	Vestibular paralysis (absent calorics)
Cognitive change	Amnestic syndrome (confabulation)
	Restlessness
	Stupor
	Coma
Hypothermia and hypotension	Caused by hypothalamic involvement (rare)

Table 3. Mental status examination

Appearance and behaviour	Well-kept individual
	Dishevelled
	Unkempt
	Drowsy
	Agitated
	Calm
	Stuporose
Speech	Vocal tremor
	Dysarthria
Mood, thought, perception and insight	Can vary depending on presentation
Cognitive change	Anterograde and retrograde amnesia
	Confabulation
	Disorientation in time
	Inability to recall the temporal sequence of events
	Long-term episodic memory impairment

Ocular signs include nystagmus (vertical and horizontal), weakness or paralysis of lateral rectus muscles (causing diplopia), weakness or paralysis of conjugate gaze, ptosis, non-reacting miotic pupils, complete loss of ocular movements, small retinal haemorrhages and papilloedema.

Ataxia is presented as an abnormality of gait and stance, wide-based stance, slow and uncertain short-stepped gait. Inability to walk without support is seen in the most severe form while the mildest form is evident in tandem walking. Vestibular paresis also plays a role in the early stages of the disease which can be elicited on caloric testing. Other manifestations include peripheral neuropathy, hypothermia, postural hypotension, tachycardia and syncope (Xiong and Daubert, 2009).

On mental status examination (*Table 3*), the general appearance can vary from a well-kept individual to a dishevelled, unkempt and drowsy patient. Behaviour can vary from agitated and restless behaviour to calm and stuporose (unresponsive). There is no characteristic speech pattern but vocal tremor or dysarthria can be identified in those withdrawing from alcohol. In those with apathy, reduced verbal content may occur. Mood can vary depending upon presentation which can be euthymic, blunted and apathetic. Thought content and form can also vary. Suicidal or homicidal ideation is generally not present but delirious patients can become self-injurious or violent. There is no characteristic perceptual disturbance but hallucinatory experiences can co-exist (Xiong and Daubert, 2009).

Cognition and sensorium vary with level of consciousness. Disorientation in time and place can be present and consistent with other forms of delirium (Gelder et al, 2006). Impaired attention and concentration can also be observed. For a patient who is not in delirium, impaired recall or orientation to date or location may occur. In those with Korsakoff syndrome, anterograde amnesia, retrograde amnesia and/or being unable to recall a temporary sequence of events can be found. Knowledge of historical facts (e.g. naming of prime ministers) is often impaired. In particular, long-term episodic memory impairment was found in patients with alcoholic Korsakoff syndrome (Duffy and O'Carroll, 2004). The patient may cover up the memory deficit by confabulating information. Confabulation in Korsakov syndrome could take two forms: confabulation of embarassment or confabulation of a fantastic nature. In confabulation of embarrassment, the patient tries to cover an exposed memory gap by an excuse relating to his/her recent behaviour. In other cases, the patient describes spontaneous adventurous experience of a fantastic nature (Sims, 2003).

Investigations

The clinical diagnosis can be confirmed by demonstration of thiamine deficiency on measurement of transke-

tolase (an enzyme dependent on thiamine pyrophosphate) activity in red cells using fresh heparinized blood (*Table 4*). The assay is performed with and without added thiamine pyrophosphate; an increase in activity of 25% with the presence of thiamine pyrophosphate demonstrates deficiency. However, the erythrocyte transketolase activity assay is not widely available. A magnetic resonance imaging scan of the brain may demonstrate symmetrical lesions around the aqueduct and the fourth ventricle which resolve after treatment with thiamine. Therefore, rapid response to treatment with intravenous thiamine is diagnostic.

Abnormal liver function may precipitate the development of Wernicke's encephalopathy by decreased conversion of thiamine to thiamine pyrophosphate and because of the decreased hepatic capacity to store thiamine.

Treatment

Water-soluble vitamins are non-toxic and can be given in large amounts if deficiency is possible. The drug is cheap and harmless (Joint Formulary Committee, 2010). However, intravenous thiamine is rarely associated with anaphylactic reactions, so appropriate precautions should be taken (*Table 5*).

Women with hyperemesis should be given lots of emotional support and reassurance. Thiamine supplementation should be given as oral thiamine hydrochloride (50 mg three times a day; the recommended daily allowance in normal pregnancy is 1.5 mg). If oral therapy cannot be tolerated, it should be given as an infusion of thiamine (100 mg diluted in 100 ml of normal saline) over 30 minutes to reduce the risk of Wernicke's encephalopathy. Alternatively, this may be given as Pabrinex, which contains thiamine hydrochloride 250 mg/10 ml and four other vitamins per pair of ampoules. Intravenous or intramuscular thiamine is required only once a week for prophylaxis for Wernicke–Korsakoff syndrome. Treatment (as opposed to prevention) requires much higher doses with the maximum of 2–3 pairs of Pabrinex ampoules three times a day. In cases of protracted hyperemesis, oral prednisolone (50 mg daily) or intravenous hydrocortisone (100 mg twice daily) often dramatically resolves symptoms. In very severe cases of hyperemesis, enteral or total parenteral nutrition may be required. This should be administered in conjunction with advice from a pharmacist and a dietician as careful monitoring is necessary. Thiamine supplementation is essential, as total parenteral nutrition has high concentrations of glucose.

Table 4. Investigations

Red cell transketolase activity
Magnetic resonance imaging of the brain
Liver function tests

Table 5. Treatment

Treatment of underlying cause
Oral thiamine 50 mg
Intramuscular thiamine 250 mg
Intravenous thiamine 100 mg
Pabrinex two ampoules (contains thiamine 250 mg)

Adequate and appropriate fluid and electrolyte replacement is important. Normal saline or Hartmann's solution is recommended – 5% dextrose saline solution and 10% dextrose solutions are dangerous, as there is a risk of the patient developing Wernicke's encephalopathy with these infusions. Antiemetics should be prescribed and given regularly, rather than on an 'as required' basis, until vomiting and nausea are under control as the common antiemetics are not teratogenic (Chiossi et al, 2006).

Ketonuria is a common finding in starvation. It can also be associated with thiamine deficiency states where ketone bodies are produced as a compensatory mechanism. Hence, persistent ketonuria despite reasonable dietary intake of carbohydrate may indicate thiamine supplementation.

Considering the pathophysiology of thiamine deficiency, it is sensible to adopt similar principles when treating a pregnant woman with severe vomiting whether or not it is hyperemesis gravidarum.

Prognosis

If treated promptly Wernicke–Korsakoff syndrome is reversible; if left it becomes an irreversible amnestic state with residual brainstem signs (White and Clare, 2005). In extreme circumstances, it can cause coma and death. Under-diagnosis of the condition has been postulated, but the prevalence of maternal mortality can be 10–20% (Sechi and Serra, 2007).

Wernicke's encephalopathy is associated with a 40% incidence of fetal death. Newborns of mothers admitted on multiple occasions for hyperemesis have significantly lower birth weights than newborn of mothers requiring a single admission (Nelson-Piercy, 2006).

Prevention

The potentially serious maternal and fetal complications of hyperemesis argue for early recognition and aggressive treatment. Women with multiple risk factors should be identified and promptly managed. Prophylactic administration of thiamine to patients with hyperemesis gravidarum and not giving intravenous fluids containing dextrose can prevent Wernicke's encephalopathy.

Conclusions

Thiamine deficiency is common in pregnancy as a result of several factors, of which excessive vomiting is the commonest. Severe thiamine deficiency which results in Wernicke–Korsakoff syndrome is a recognized cause of

maternal death. Recognition of high-risk patients, making a clinical diagnosis, thiamine therapy, avoidance of dextrose and treating the cause are all important to prevent complications. BJHM

Conflict of interest: none.

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KEY POINTS

- Excessive vomiting in pregnancy is associated with Wernicke's encephalopathy.
- Wernicke's encephalopathy is associated with increased risk of maternal death.
- The underlying cause is thiamine (vitamin B1) deficiency.
- Wernicke's encephalopathy is a clinical diagnosis although investigations might be useful.
- Treatment with thiamine is safe and effective, preventing the disease as well as death.