Chapter 14
Wernicke's Encephalopathy

Maryam R. Kashi, George I. Henderson, and Steven Schenker

Introduction

Wernicke's encephalopathy (WE) is a potentially reversible metabolic brain dysfunction resulting from thiamine deficiency. It is generally characterized by ataxia, ophthalmoplegia and global confusion. Described in Berlin in 1881 by Carl Wernicke, it was initially known as *polioencephalitis hemorrhagica superioris* and considered a fatal syndrome. The first reported cases were three patients, two with alcoholism and one with persistent vomiting after the ingestion of sulfuric acid in a suicide attempt. The common feature shared by these cases upon post-mortem exam consisted of punctate hemorrhages in the grey matter of the walls of the third and fourth ventricles and mammillary bodies (Cirignotta *et al.*, 2000; Truswell, 2000). In 1935, Strauss discovered that the cause of Wernicke's findings was vitamin B1 (thiamine) deficiency (Chiossi *et al.*, 2006). Bonhoeffer posited that Wernicke's encephalopathy and the psychosis described by Korsakoff actually represented two phases of the same pathological process (Cirignotta *et al.*, 2000). The observation that Wernicke's encephalopathy and Korsakoff's psychosis have identical neuropathology supported this belief (Charness, 1999). Thus Wernicke's encephalopathy (WE) and Korsakoff's psychosis (KP) are often used interchangeably as the Wernicke-Korsakoff Syndrome (WKS).

Korsakoff psychosis is a chronic amnestic state, characterized by retrograde amnesia (loss of memory), anterograde amnesia (defective learning) and confabulation. Loss of short-term memory is a predominant feature, while immediate and long-term memories are usually intact. (Harrison *et al.*, 2006; Chiossi *et al.*, 2005; Sivolap, 2005). Patients with KP have difficulty remembering events and facts that occur after the onset of disease (Hochhalter and Joseph, 2001). It occurs most commonly in patients with WE, usually secondary to alcoholism, but may be seen in patients without a previous diagnosis of WE (Truswell, 2000). It has been suggested that some of these patients may have had subacute cases of WE, where signs and symptoms were either mild or absent. Nevertheless, on autopsy, patients with KP have the same brain pathology as patients with WE, as mentioned earlier (Charness, 2006).

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Pathologically, WE may be classified into acute (17%), subacute (17%) and chronic (66%) states. It has been postulated that WE may be a progressive disorder, where multiple acute and/or subclinical episodes of thiamine deficiency cause cumulative damage. These subclinical events may be devoid of the traditional symptoms associated with WE (Gui *et al.*, 2006; Harper, 1983). This may explain the findings of brain lesions at postmortem without antecedent symptoms in some patients. Analogously, Korsakoff's psychosis may occur in patients who have experienced multiple acute and/or subclinical events of WE. This may explain the discrepancy between the relatively high numbers of alcoholic patients who develop Korsakoff's psychosis as compared to nonalcoholic patients. There are at least two hypotheses to explain this observation. The first hypothesis presumes that the latter group's exposure to a thiamine-deficient state was a single event, while the former group is likely to have had long-standing thiamine deficiency and/or multiple events of WE, increasing their chances of developing KP (Homewood and Bond, 1999). The second hypothesis is that perhaps ethanol neurotoxicity and thiamine deficiency work in concert in the development of KP (Charness, 2006).

Victor *et al.* (1989), in classic studies, followed 186 alcoholic patients with Wernicke's encephalopathy for up to ten years and documented that 84% developed Korsakoff's syndrome. A subsequent study of 32 alcoholic patients followed for a period of 33 months showed the rate of progression to KP to be 56% (Wood *et al.*, 1984). Full recovery from Korsakoff's psychosis occured in only 20%; the majority of KP patients required some level of supervision and social support (Reuler *et al.*, 1985; Charness, 2006).

Wernicke's encephalopathy is associated with a mortality rate of 10–20%, predominantly as a result of sepsis, respiratory infection and decompensated liver disease; Korsakoff's psychosis is associated with a mortality rate of approximately 17% (Harrison *et al.*, 2006; Ogershok *et al.*, 2002; Merkin-Zaborsky *et al.*, 2001).

Prevalence

The prevalence rates of 0.8% –2.8% for WE come mainly from four autopsy-based studies: Norway (0.8%), New York (1.7%), Cleveland (2.2%) and Australia (2.8%) (Harper, 1983; Ogershok *et al.*, 2002). Australia's higher prevalence of WE was puzzling, as the country is not ranked high on the world league table of alcohol consumption. After conducting interviews with patients in alcohol rehabilitation units, Price concluded that Australian alcoholics were more likely to lack female social support, which may otherwise provide them with food containing thiamine (Truswell, 2000). Seventy-five percent of patients are male and the peak age incidence is in the sixth decade (41%) (Harper, 1983). Wernicke's encephalopathy remains a profoundly under-diagnosed disease, which if left untreated can progress to Korsakoff syndrome or death, as a result of irreversible cytotoxic effects (Loh *et al.*, 2004; Weidauer *et al.*, 2004). Harper found that only

20% of cases reviewed in a necropsy study had been diagnosed with WE or Wernicke-Korsakoff syndrome prior to death (Harper, 1983). Thus a high index of suspicion is the key to diagnosis.

Clinical Features

The classic triad of symptoms in WE includes ophthalmoplegia, ataxia and global confusion (see Table 14.1). However, the clinical presentation is often incomplete (Foster *et al.*, 2005). In a retrospective study, it was found that only 16.5% of patients exhibited all three signs and 19% exhibited none of these (Harper *et al.*, 1986). One study found nystagmus to be present in 85%, bilateral paralysis of the lateral rectus muscles in 54% and conjugate gaze palsies in 45% of cases (Ogershok *et al.*, 2002)). Other reported symptoms include apathy, lightheadedness, disorientation, poor memory, diplopia, inability to stand, nausea, vomiting and coma (Liu *et al.*, 2006; Giglioli *et al.*, 2004; Morcos *et al.*, 2004; Harper *et al.*, 1986; Ogershok *et al.*, 2002). In addition, WE can affect the sympathetic system, resulting in postural hypotension and syncope, and the temperature-regulating center, resulting in mild hypothermia (Worden, 1984; Reuler *et al.*, 1985). The lag time from onset of thiamine-deficiency to the start of symptoms is approximately 4–6 weeks (Harrison et al., 2006). Symptoms may range from a period of 2 days to 2 weeks before presentation for evaluation (Giglioli *et al.*, 2004; Lacasse and Lum, 2004).

Wernicke's encephalopathy is most commonly associated with alcoholism. It has been suggested that there may be a synergistic effect of alcoholism and thiamine deficiency, where a brain affected by alcoholism may be more susceptible to injury caused by thiamine deficiency (Homewood and Bond, 1999). However, WE may be found in any clinical state associated with malnutrition or thiamine deficiency

Table 14.1 Clinical features of wernicke's encephalopathy

Classical Symptoms	Other Associated Symptoms
Ataxia	Apathy
Global Confusion	lightheadedness
Ophthalmoplegia	disorientation
	poor memory
	unsteady gait
	diplopia
	vision impairment
	nystagmus, inability to stand
	nausea
	vomiting
	coma
	hypothermia

Table 14.2 Conditions associated with wernicke's encephalopathy

Anorexia Nervosa (Harrison *et al.*, 2006; Morcos *et al.*, 2004; Ogershok *et al.*, 2002)	Malignancy (Weidauer *et al.*, 2004; Ogershok *et al.*, 2002)
Chronic alcoholism	Prolonged parenteral feeding without Thiamine supplementation (Morcos *et al.*, 2004; D'Aprile *et al.*, 2000)
Diarrheal Disorders (Celik and Kaya, 2004)	Prolonged starvation/Malnutrition (Attard *et al.*, 2006; Ogershok *et al.*, 2002)
Gastric/Bariatric surgery (Attard *et al.*, 2006; Loh *et al.*, 2004; Cirignotta *et al.*, 2000)	Regional enteritis (Ogershok *et al.*, 2002)
Hemodialysis/Peritoneal dialysis (Ogershok *et al.*, 2002; Merkin-Zaborsky *et al.*, 2001)	Refeeding after starvation (Ogershok *et al.*, 2002)
HIV/AIDS (Ogershok *et al.*, 2002)	Thyrotoxicosis (Ogershok *et al.*, 2002)
HIV Encephalopathy (Morcos *et al.*, 2004)	Uremia (Ogershok *et al.*, 2002)
Hyperemesis gravidarum (Harrison *et al.*, 2006)	
Malabsorption syndromes (Ogershok et al., 2002)	

Table 14.3 Possible causes of thiamine deficiency in chronic alcoholism

1. Inadequate thiamine intake
2. Decreased activation of thiamine to thiamine pyrophosphate
3. Reduced hepatic storage of thiamine
4. Inhibition of intestinal thiamine transport
5. Impairment of thiamine absorption due to ethanol-related nutritional deficiency states

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(see Table 14.2), including hyperemesis gravidarum (Chiossi *et al.*, 2006), anorexia nervosa (Morcos et al., 2004), prolonged parenteral feeding without micronutrient supplementation (Attard *et al.*, 2006), renal disease with hemodialysis or peritoneal dialysis and gastric or bariatric surgery (Attard *et al.*, 2006; Worden and Allen, 2006; Loh et al., 2004; Cirignotta et al., 2000; Ogershok et al., 2002). Although studies have found that 23–50% of cases are actually not associated with alcohol abuse, the index of suspicion for thiamine deficiency is still low in non-alcoholic patients (Ogershok *et al.*, 2002).

The incidence of thiamine deficiency in alcoholics is 30–80% (Homewood and Bond, 1999). Factors that promote thiamine deficiency in alcoholics include poor thiamine intake, decreased activation of thiamine to thiamine pyrophosphate(TPP), decreased hepatic storage, decreased intestinal thiamine transport and impairment of thiamine absorption (see Table 14.3) (Breen *et al*, 1985; Hoyumpa, 1980). Although thiamine is stored in various sites, including skeletal muscles, heart, kidneys and brain, the liver remains the main storage site. Due to the reasons cited above, hepatic thiamine content may be reduced by 73% in patients with severe, chronic alcoholic liver disease. In addition, ethanol has been shown to promote thiamine release from the liver (Hoyumpa, 1980).

Chiossi *et al.* (2006) reviewed 49 case reports of WE due to hyperemesis gravidarum. The duration of vomiting and/or poor intake was 7.7 +/ − 2.8 weeks. The mean gestational age was 14.3 +/ − 3.4 weeks and the amount of weight loss ranged from 6–25 kg. Thirty-two percent of these patients were primigravida (Chiossi *et al.*, 2006). In laboratory rats, thiamine deficiency is a known cause of intrauterine growth retardation. In a German study, lower erythrocyte thiamine concentrations were found in patients whose pregnancies were complicated by intrauterine growth retardation than in patients with normal pregnancies (Heinze and Weber, 1990), although a causal relationship is uncertain.

Chronic renal failure patients on hemodialysis and peritoneal dialysis are at risk for thiamine deficiency due to inadequate nutrition in part and possible thiamine loss during the dialysis process. Renal failure patients are often on a diet restricted in protein and potassium, which increases the risk of thiamine deficiency (Masud, 2002; Piccoli *et al.*, 2006). Studies with detailed dietary surveys have shown poor oral intake of thiamine in chronic renal failure patients (Hung et al., 2001). There is no convincing evidence that thiamine levels are significantly altered by either hemodialysis or peritoneal dialysis (Reuler *et al.*, 1985). DeBari *et al.* (1984) measured thiamine levels of granulocytes, erythrocytes and plasma. They found no significant differences in thiamine levels in dialysis patients compared to controls. Further research in this area would benefit chronic renal failure patients and help determine possible need for supplementation of water-soluble vitamins.

Due to the obesity epidemic in the United States, bariatric surgery is becoming increasingly more common. As a result, nutrient malabsorption is becoming more common as well. A common procedure, Roux-en-y gastric bypass (RYGBP), causes both food restriction and malabsorption. Malabsorption is caused by the bypass of the distal stomach, duodenum and the first part of the jejunum. Vomiting is a common side effect of RYGBP and vitamin B12 and iron deficiency are frequently seen. Thiamine deficiency may occur in this setting as a result of bypass of the duodenum, as this is where thiamine is predominantly absorbed (Worden and Allen, 2006). Some authors routinely advocate starting parenteral thiamine administration six weeks postoperatively in malnourished patients (Loh *et al.*, 2004). Prolonged parenteral feeding without thiamine supplementation is a well-documented cause of Wernicke's encephalopathy.

Administration of intravenous glucose activates glycolysis, a process which utilizes thiamine and may enhance thiamine deficiency (Koguchi *et al.*, 2004). Thus common emergency room practice includes the administration of intravenous thiamine before intravenous glucose in order to prevent the precipitation of WE. Whether or not this practice is warranted is somewhat controversial. In a review of 49 published cases of *hyperemesis gravidarum* as the leading cause of WE, Chiossi et al. felt that approximately 30% of the cases were provoked by intravenous glucose administration without thiamine (Chiossi *et al.*, 2006). Many other case reports have also noted such a phenomenon but good evidence-based studies are lacking. Harrison notes this to be a "theoretical concern. " (Harrison *et al.*, 2006). Pazirandeh et al. (2006) point out that cellular thiamine uptake is actually slower than glucose uptake. As such, cellular thiamine repletion may not occur prior to cellular glucose exposure.

Wernicke's encephalopathy may appear inconspicuously in psychiatric patients, as it may be obscured by mental illness. Patients with schizophrenia, for example, may be particularly at risk due to poor dietary intake, high rates of homelessness and high prevalence of alcoholism (Harrison *et al.*, 2006).

Infantile WE may be found in developing countries, primarily among breast-fed infants, usually in the second to fifth months of development. Wernicke's encephalopathy is very rare in developed nations. However, in 2003, Israel was faced with an epidemic of WE due to a batch of defective soy-based vegetarian infant formula. WE was documented in 20 out of an estimated 3500 infants who were fed the formula, later found to be deficient in thiamine (Kesler *et al.*, 2005).

Diagnosis

Although the diagnosis of WE is generally considered to be a clinical one, supporting laboratory tests and neuroimaging data may be important. Generally, routine laboratory tests, such as liver profile and renal function, urinalysis, chest x-rays, electrocardiograms and echocardiograms are normal, as are cerebrospinal fluid tests. Serum lactic acid, however, has been shown to be elevated in the setting of thiamine deficiency, particularly in children (Liu *et al.*, 2006; Attard *et al.*, 2006; Weidauer *et al.*, 2004). In one case study, an electromyelogram showed diffuse sensorimotor neuropathy (Cirignotta *et al.*, 2000); in another case, an electroencephalography revealed diffuse slow activity or dysrhythmia (Chiossi *et al.*, 2006).

Serum thiamine levels may be misleading and thus should not be employed for the diagnosis of Wernicke's encephalopathy. There are two laboratory tests which are used as surrogates for body thiamine stores. The erythrocyte transketolase test (ETKA) is a reflection of thiamine reserves at a cellular level. The thiamine pyrophosphate effect (TPPE) test, expressed as a coefficient, is a measure of transketolase activity before and after the addition of thiamine. Values before added thiamine reflect the amount of coenzyme present in the cell; the values measured after thiamine addition is a reflection of the amount of apoenzyme present that lacks a coenzyme. Diagnosis is made by either a low ETKA and/or a high TPPE. Normal TPPE values range from 0% –14%. TPPE values between 15% and 24% signify marginal thiamine deficiency and values greater than 25% signify severe deficiency (Kesler *et al.*, 2005; Chiossi *et al.*, 2006). Unfortunately, ETKA and TPPE are not readily commercially available in the United States. Thus patients should be treated once suspected clinically of WE. Clinical response to treatment is the ultimate persuasive diagnostic test.

By performing thorough clinical histories, neurological and psychological exams, as well as pathological evaluations, Caine *et al.* (1997) developed a set of diagnostic criteria for WE in alcoholic patients. The diagnostic criteria, published in 1997, require two of the following four signs for the diagnosis of WE: oculomotor abnormalities, malnutrition, cerebellar dysfunction and either mild memory impairment or altered mental status (see Table 14.4). Validity testing of this approach

Table 14.4 Caine's diagnostic criteria for wernicke's encephalopathy

Two of the following criteria must be met:
1. Dietary deficiency
2. Oculomotor abnormality
3. Cerebellar dysfunction
4. Altered mental status or mild memory impairment

demonstrated improved diagnostic sensitivity from 31% (using the classic triad) to about 100%. They report that sensitivity decreased to 50% in patients with concurrent hepatic encephalopathy. This is not unexpected, as two of the elements in the above criteria, malnutrition and altered mental status, are commonly seen in patients with hepatic encephalopathy. Proper management of these conditions (i.e. serum ammonia levels and response to appropriate therapy) should elucidate the proper diagnosis. The Caine criteria were developed based on studies of patients with alcoholism and should not be applied, at present, to a general population. Future studies should assess these criteria in a nonalcoholic population.

Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) have been studied with regard to their evaluation of WE. CT appears to be helpful only in cases with hemorrhagic lesions, which include only approximately 5% of cases (Chiossi *et al.*, 2006; Mascalchi *et al.*, 1999). Computed tomography was reported by Antunez *et al.* (1998) to have quite a low sensitivity (13%) in the diagnosis of WE.

MRI sequences typically include, pre- and post-contrast (gadolinium) T1-weighted images with gadolinium, T2-weighted images, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) mapping. MRI has a sensitivity and specificity of 53% and 93%, respectively, for WE (Ogershok *et al.*, 2002). The sensitivity may actually be higher, but MRI is often performed after the patient has been suspected of WE and empirically treated, resulting in a non-diagnostic study (Celik and Kaya, 2004). Good correlation has been found between contrast mediated magnetic resonance imaging (MRI) and neuropathological findings (Liu *et al.*, 2006). Classically, T2-weighted and FLAIR MRI images reveal symmetrical increased signal intensity of areas including the third paraventricular regions of the thalamus and hypothalamus, periaqueductal regions of the midbrain and mammillary bodies. These lesions may sometimes be enhanced with gadolinium on T1-weighted images during an acute event and may dissipate with treatment (Chiossi *et al*, 2006; Mascalchi *et al.*, 1999; Doherty *et al.*, 2002; Halavaara *et al.*, 2003). In one case, mammillary body enhancement was the only sign of acute WE (Shogry and Curnes, 1994). FLAIR sequences are reviewed

to ensure that the cerebrospinal fluid has not masked high signal lesions on T2-weighted imaging (Chung *et al.*, 2003). The chronic stage of WE may be depicted by brain atrophy and diffuse signal-intensity changes in the cerebral white matter (White *et al.*, 2005).

Some of the lesion identified on MRI may be seen in other conditions, such as inferolateral and anterolateral thalamic infarcts, multiple sclerosis, Cytomegalovirus encephalitis, Behcet's disease, primary cerebral lymphoma, central pontine myelinosis, Lyme disease, Leigh's disease and variant Creutzfeldt-Jokob disease. These conditions are usually excluded from the differential diagnosis based both on their asymmetric distribution and the clinical setting (Weidauer *et al.*, 2004; Chung *et al.*, 2003). Neuroimaging may be a very useful tool in the diagnosis of WE; however, it is important to note that the absence of signs on neuroimaging does not exclude the diagnosis (Antunez *et al.*, 1998; Celik and Kaya, 2004).

Although there is insufficient evidence to suggest the presence of cytotoxic edema in acute WE, there is good evidence for vasogenic edema (Liu *et al.*, 2006). The advantage of DWI over T2-weighted and FLAIR imaging is its ability to better distinguish between cytotoxic and vasogenic edema (Chiossi *et al.*, 2006; Chung *et al.*, 2003). DWI, in conjunction with ADC mapping, is particularly useful, as it is the most sensitive method for diagnosing early injury, i.e. vasogenic edema, before the onset of necrosis, thus facilitating early diagnosis of WE (Doherty *et al.*, 2002; Halavaara *et al.*, 2003). Cytotoxic edema is represented by high intensity signal on DWI with corresponding low signal on ADC mapping. Vasogenic edema, however, will show high signal intensity on both DWI and ADC mapping (Weidauer *et al.*, 2004).

Single-photon emission computed tomography (SPECT) imaging has also been evaluated and at least one study has found it to be useful in cases where conventional MRI may be non-diagnostic (Celik and Kaya, 2004).

Pathology

Wernicke's encephalopathy, which affects the brainstem, white matter and cortex, has a characteristic appearance on autopsy (Celik and Kaya, 2004). The acute stage of WE is characterized by the inability to maintain proper osmotic gradients of cell membranes, promoting intracellular swelling and red blood cell extravasation into the perivascular space. This stage is distinguished by marked vascular dilatation, endothelial swelling and neuronal demyelinization. The chronic stage is marked by mammillary body atrophy, as well as, loss of neuropil with fibrillary astrocytosis (Weidauer *et al.*, 2004; D'Aprile *et al.*, 2000; Homewood and Bond, 1999). Neurons, however, are generally spared (Liu *et al.*, 2006; Gui *et al.*, 2006; Halavaara *et al.*, 2003). Classic neuropathological findings include petechial hemorrhages of blood vessels and small, symmetric necrotic lesions in the paraventricular areas of the thalamus, hypothalamus, mammillary bodies, periaqueductal area of the midbrain and cerebellum (McEntee, 1997; Chung *et al.*, 2003; Caine *et al.*, 1997).

Table 14.5 Macroscopic and microscopic findings of wernicke's encephalopathy on autopsy

Macroscopic lesions	Microscopic lesions
Ventricular dilatation (34%)	Mammillary bodies (99%)
Mammillary body atrophy (75%)	Third ventricular wall (61%)
Cerebellar vermal atrophy (34%)	Thalamus (61%)
Cerebellar atrophy (21%)	Midbrain (50%)
Paraventricular atrophy (5%)	Pons (50%)
	Medulla (33%)

(Harper, 1983)

It has been proposed that perhaps the paraventricular regions are more susceptible to thiamine deficiency because they have a higher rate of glucose and oxidative metabolism which require thiamine (Lacasse and Lum, 2004). The most consistent pathological findings, found in 75% of the cases, are mammillary body atrophy and brownish discoloration (Liu *et al.*, 2006; Harper, 1983). Although a small proportion of patients may have normal sized mammillary bodies, almost all have microscopic mammillary body lesions (Charness, 1999). Macrohemorrhage is found in approximately 5% of cases (Mascalchi *et al.*, 1999). Table 14.5 shows Harper's macroscopic and microscopic autopsy findings in WE (Harper, 1983).

Role of Thiamine

Thiamine (B1) is an essential coenzyme for enzymes involved in Kreb's cycle (including pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase), lipid metabolism/amino acid production (transketolase) and neurotransmitter synthesis—acetylcholine and GABA (2-oxo-glutarate dehydrogenase) (Chiossi *et al.*, 2006). A commonly found water-soluble vitamin, it is found in lean pork, poultry, fish, eggs, liver, wheat germ, whole grains, beans, peas and nuts. Fruits, vegetable and dairy products are not good sources of thiamine (Table 14.6) Alcoholic beverages have virtually no thiamine (Table 14.7) (Lonsdale, 2006). However, it has been suggested that small amounts of thiamine exist in German and Australian beer (Price and Kerr, 1985). The human daily requirement of thiamine is 1.0–1.5 mg per day but this requirement is increased in states of pregnancy, lactation, thyrotoxicosis and fever. Body stores are approximately 25–30 mg and are found predominantly in skeletal muscles, heart, liver, kidneys and brain (Lacasse and Lum, 2004). These reserves are sufficient for only 2–3 weeks without continued intake (Gui *et al.*, 2006; Kesler *et al.*, 2005). Thiamine, which is excreted in the urine, has a half-life of approximately 10–20 days (Pazirandeh *et al.*, 2006). Loss of thiamine is accelerated by diuretic therapy and may be inactivated by polyphenol containing compounds found in coffee and tea (Lonsdale, 2006). Malabsorption may occur with alcoholism, with gastric surgery and with folate deficiency (Lacasse and Lum,

Table 14.6 High thiamine foods: thiamine content/100g food product

Lean Pork (avg of trimmed retail cuts, loin, and shoulder blade, lean only, cooked)	0.873 mg
Poultry (cooked):	
Turkey	0.06 mg
Chicken	0.069 mg
Fish (cooked):	
Tuna	0.278 mg
Catfish	0.42 mg
Tilapia	0.093 mg
Whitefish (mixed species)	0.171 mg
Salmon	0.34 mg
Eggs (raw)	0.069 mg
Beef Liver (cooked)	0.194 mg
Chicken Liver (cooked)	0.291 mg
Wheat germ	1.882 mg
Beans (pinto, cooked)	0.193 mg
Peas (cooked)	0.259 mg
Soybeans (cooked)	0.155 mg
Kidney (beef)	0.16 mg
Nuts	0.2 mg
Whole grains (dry):	
Whole wheat flour	0.447 mg
Bulgur	0.232 mg
Oats	0.763 mg
Whole cornmeal	0.385 mg
Buckwheat	0.101 mg
Brown rice	0.413 mg

(The Food Processor SQL, 2006)

Table 14.7 Thiamine content in alcoholic beverages

Standard beer (12 oz) - 0.00 mg
Red wine (4 oz) - 0.01 mg
White wine (4 oz) - 0.01 mg
Tequila/Gin/Bourbon/Whiskey/Vodka (80 proof/1.5 oz) - 0.00 mg

(The Food Processor SQL, 2006)

2004; Price and Kerr, 1985). Alcohol has been found to interfere with the active transport of thiamine in the gastrointestinal system, at least in rodents (Kumar *et al.*, 2000). Thiamine absorption may be significantly decreased in the setting of folate depletion but may return to normal with 4–6 weeks of folate repletion therapy. A deficiency in magnesium, required for the conversion of thiamine to thiamine pyrophosphate, may also cause thiamine deficiency (Bishai and Bozzetti, 1986; Lonsdale, 2006).

Medications postulated to affect body stores of thiamine include: 5-fluorouracil (Heier and Dornish, 1989), loop diuretics (Brady et al., 1995; Seligmann et al., 1991) and dilantin (Patrini *et al.*, 1993; Botez *et al.*, 1993).

Thiamine Absorption

Dietary thiamine exists primarily in the form of thiamine pyrophosphate (TPP), which must be hydrolyzed to free thiamine, before absorption in the small bowel (Dudeja et al., 2001). In the small bowel, thiamine absorption occurs by two processes: passive and active transport. Passive transport occurs only in the presence of high thiamine concentrations, and actually blocks the active transport process. Low doses of thiamine are absorbed by active transport (Rindi and Ventura, 1972). The details of this absorption mechanism are still not completely clear. Dudeja et al. have performed multiple studies evaluating jejunal thiamine absorption at both the brush border membrane (BBM) and the basolateral membrane (BLM). In one study, they found that human intestinal BBM absorption of thiamine is a carrier-mediated process, which is sodium-independent, pH-dependent and amiloride-sensitive. They have also proposed the possibility of a thiamine—/H+ exchange mechanism (Dudeja *et al.*, 2001). In a study of thiamine absorption in jejunal BLM, Dudeja et al. found the transport mechanism to be a pH-dependent and amiloride-sensitive carrier-mediated process (Dudeja et al., 2003). SCL19A2, believed to be a human thiamine transporter, has been shown to be expressed in all gastrointestinal tissues, with the greatest level of expression found in the liver. Reidling et al. have discovered that the minimal promoter region needed for basal activity of SLC19A2 gene is encoded between −356 and −36 (Reidling *et al.*, 2002).

Breen *et al.* evaluated the influence of acute alcohol perfusion on small bowel absorption of thiamine. They found that alcohol did not significantly decrease thiamine uptake in the jejunum, although there was a trend to lower absorption with alcohol perfusion (Breen et al., 1985). Holzbach evaluated thiamine absorption in patients after 3 days and after 4 weeks of resolution of acute delirium tremens (DT). He found no significant difference in thiamine absorption between normal patients and those with recent delirium tremens. There was, however, a significant increase in thiamine absorption 4 weeks after DT as compared to values obtained shortly (3 days) after DT. They propose the possibility of abnormal thiamine absorption in DT. It is noteworthy that the patients with visual hallucinations had lower thiamine absorption levels than those who did not have this symptom (Holzbach, 1996). Tomasulo studied thiamine deficiency in severely alcoholic patients admitted to the hospital. Forty-three percent of these patients had DT. He measured radioactive thiamine in both urine and stool and found significant differences between controls and alcoholics. The labeled thiamine excreted in 24-hour urine collections of controls and alcoholics were 45.8% and 25.3%, respectively. The reciprocal findings of stool in controls and alcoholics were 4.0% and 21.0%, respectively (Tomasulo *et al.*, 1968). Studies by Thomson *et al.* (1968) also provide evidence that chronic

alcohol abuse may decrease thiamine absorption. These various studies differ, not only in their methodologies, but also in their subject populations. Breen's study assessed the effects of acute alcohol while the latter three studied chronic alcoholics. This area clearly deserves further research.

Pathogenesis of Wernicke's Encephalopathy

Serious attempts to determine the mechanism(s) of this disorder have been ongoing for at least 70 years (Peters, 1969). There are many aspects of WE which should make this task relatively easy. First, the clinical picture of this disorder is well characterized, can be readily diagnosed and is relatively specific. Second, the pathology of this entity is elegantly described and imaging by MRI, when present, is characteristic. Third, there are animal models readily available which should permit a biochemical/pathologic dissection of the problem. Fourth, the specific deficiency, a decrease of vitamin B_1, responsible for the experimental and clinical findings of WE is well-known. Most importantly, the experimentally induced and clinical syndromes are often readily reversible (if seen early) by the administration of thiamine.

With such an extensive knowledge base, what is the present state of our understanding of the mechanisms of this disorder? Not unexpectedly, initial studies, primarily in experimental animal models, focused on the known metabolic pathways which involve thiamine. Indeed, the classical studies of Peters in 1930 (Peters, 1969) showed lactate accumulation in the brainstem of thiamine deficient birds with normalization of this in vitro when thiamine was added to the tissue. This led to the concept of "the biochemical lesion" of the brain in thiamine deficiency. The enzymes which depend on thiamine are shown in Fig. 14.1. They are transketolase, pyruvate and α-ketoglutarate dehydrogenase. Transketolase is involved in the pentose phosphate pathway needed to form nucleic acids and membrane lipids, including myelin. The ketoacid dehydrogenases are key enzymes of the Krebs cycle needed for energy (ATP) synthesis and also to form acetylcholine via Acetyl CoA synthesis. Decrease in activity of this cycle would result in anaerobic metabolism and lead to lactate formation (i.e., tissue acidosis) (Fig. 14.1).

Indeed, studies in animal models of thiamine deficiency and a small number of postmortem human brain specimens have shown that transketolase and α-ketoglutarate dehydrogenase (but not consistently pyruvate dehydrogenase) were depressed. Perhaps the largest and earliest fall was seen in brain transketolase; however, when the neurological signs were reversed with thiamine there was no concomitant improvement in transketolase which rose only slightly (McCandless and Schenker, 1968). Moreover, glucose flux through the pentose phosphate pathway (dependent on transketolase) did not decrease in severe thiamine deficiency and ribose-5-phosphate (a key intermediate in the pentose cycle) did not fall (McCandless *et al.*, 1976; McCandless, 1982). Thus, the current view is that a low transketolase is a marker of thiamine deficiency, but is likely not to be causal in the acute neurological deficits seen in thiamine deficiency (McCandless, 1982; Hazell *et al.*, 1998). The possible

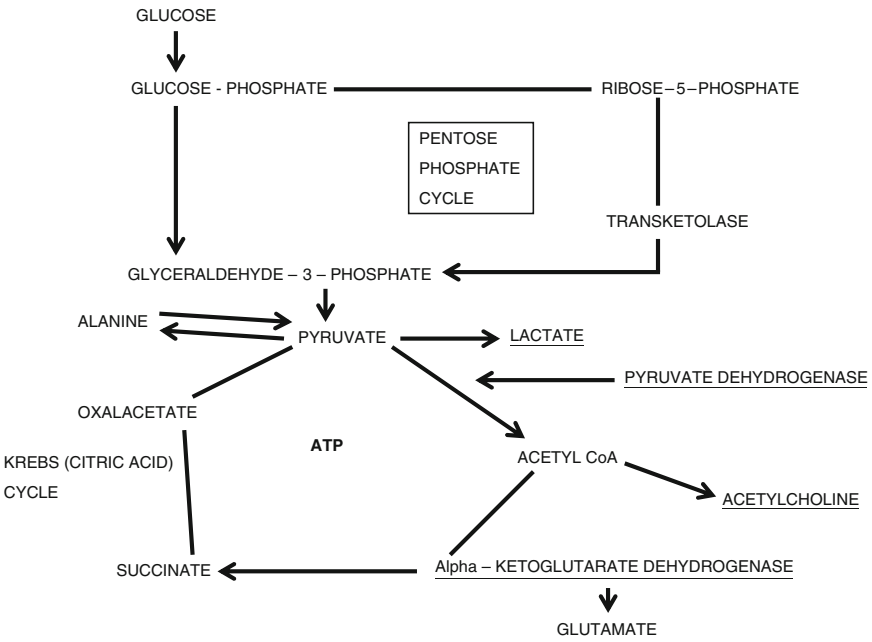

Fig. 14.1 Enzymes which depend on thiamine: there are transketolase, pyruvate and alpha-ketoglutarate dehydrogenase (see text)

effects of prolonged transketolase depression, as with chronic thiamine deficit, are uncertain (Hazell *et al.*, 1998).

Data on the role of acetylcholine deficit in thiamine deficiency are conflicting, but most recent studies do not favor a significant decrease in the synthesis of this neurotransmitter (Hazell *et al.*, 1998; Vorhees *et al.*, 1977). This would be consistent with normal pyruvate dehydrogenase activity in experimental thiamine deficiency, which should not, therefore, result in a lower Acetyl CoA level as a precursor to acetylcholine.

Perhaps the most likely mechanism of low thiamine-induced brain injury has revolved around impairment of the Krebs' cycle and deficit in available ATP (Desjardins and Butterworth, 2005). This could readily lead to apoptosis and necrosis of neurons, as has been described in such patients (Vorhees *et al.*, 1977). In this context, the data on pyruvate dehydrogenase are somewhat difficult to interpret. Postmortem brain from patients with Wernicke's encephalopathy did show a major decrease in pyruvate dehydrogenase, albeit in only a few specimens (Butterworth *et al.*, 1993). However, this was not corroborated in experimental models of this syndrome (Desjardins and Butterworth, 2005; Butterworth et al., 1993). By contrast a major decrease in brain α-ketoglutarate dehydrogenase was seen in every type of thiamine deficiency (Desjardins and Butterworth, 2005; Butterworth et al., 1993). Moreover, an impairment in this enzyme could readily explain an increase in brain lactate, due to anaerobic metabolism, and this has been observed uniformly, even

as far back as 1930 (Peters, 1969; McCandless and Schenker, 1968; Desjardins and Butterworth, 2005). The major concern about the Krebs cycle deficit concept has been a difficulty in documenting consistently an impairment in brain energy stores, both ATP and phosphocreatine (PCr). Multiple studies in the brain of animals with thiamine deficiency have not shown a decrease in ATP or PCr, even when assayed in brain areas (brainstem and lateral vestibular nucleus) felt to be most affected (McCandless and Schenker, 1968; McCandless, 1982; McEntee, 1997; Holowach et al., 1968). The only exception was a study by Aikawa et al. (1984), who showed a small decrease in ATP and PCr in some parts of rat brain after exposure to pyrithiamine (thiamine antagonist). The functional significance of this small (~10%) drop in ATP is not known, but in our view is unlikely to be important. McCandless has shown *increased* levels of both ATP and PCr in the lateral vestibular nucleus of such animals, as well as in rats rendered thiamine deficient by dietary means (McCandless, 1982; McCandless and Schwartzenburg, 1981). The higher energy stores reverted to normal on restoration of thiamine. These latter data suggest that energy utilization was impaired during the symptomatic stage. Formal energy turnover studies in critically affected brain areas have not been done, to our knowledge. Clearly, the role of an impaired Krebs cycle in the pathogenesis of Wernicke's encephalopathy is unresolved.

A number of other mechanisms have been suggested recently for the brain damage caused by thiamine lack. One stipulates that an excess of extracellular glutamate induces increased neurotoxicity (McEntee, 1997). The evidence for this are increased concentrations of glutamate in the extracellular fluid (dialysate) in brains of pyrithiamine-treated rats and decrease in glutamate transporters in astrocytes of these animals (Desjardins and Butterworth, 2005; McEntee, 1997). Another concept is that of oxidative stress via the production of reactive oxygen species and/or increased expression of endothelial nitric oxide synthase (Desjardins and Butterworth, 2005). Finally, neuropathological studies in both animal models and postmortem brain sections in patients with Wernicke's have shown proliferation of astroglial cells, especially in the early stages of thiamine deficiency (Desjardins and Butterworth, 2005). Based on the known protective effects of astrocytes for neurons, this rather suggests that these cells may be activated in that setting, perhaps to provide GSH as an antioxidant (Rathinam et al., 2006). Overall, it appears that the precise mechanism by which thiamine deficiency causes brain injury is unknown. Conceivably multiple factors may be operative.

Another important question relates to the selective sensitivity of specific brain areas to thiamine deficiency. The basis for this has been discussed in terms of differences in regional metabolism, antioxidant status, or differences in thiamine turnover, but without actual data (Desjardins and Butterworth, 2005). Similar regional sensitivity has been seen with bilirubin and copper deposition/damage without explanation. Much remains to be learned.

It has been suggested that there may be a predisposition to WE in some patients, presumably on a genetic basis. Indeed, a variant of transketolase has been reported in fibroblasts of patients with WE (Blass and Gibson, 1977; Nixon *et al.*, 1984). It was proposed that this may increase the requirements of thiamine in such patients,

and thus possibly make them more susceptible to thiamine deficits (Martin *et al.*, 1995). However, this concept has not been further verified (Kaufmann *et al.*, 1987; Blansjaar *et al.*, 1991). The authors are unaware of any reported familial clustering of WE, and transketolase is not felt now to be an enzyme primarily causally involved in the pathogenesis of this cerebral disorder. Studies of possible variants in other enzymes involved in thiamine metabolism have not been reported.

Treatment

Wernicke's encephalopathy is a potentially fatal but also reversible medical emergency if diagnosed and treated in the acute stage. Treatment includes supportive measures, as well as thiamine replacement; however, the basic questions of thiamine dose, frequency, route and length of treatment remain unclear (Morcos *et al.*, 2004). The Cochrane Collaboration (2007) sought to evaluate the evidence available for the use of thiamine in the treatment of Wernicke-Korsakoff Syndrome due to alcohol abuse. There were actually no studies that addressed this specifically but the Cochrane group identified one published randomized controlled study, by Ambrose et al., that compared the effects of various doses of thiamine therapy in alcoholic patients without overt clinical signs of WKS (Day *et al.*, 2004). In 2001, Ambrose evaluated the effects of differing doses of thiamine hydrochloride (5, 20, 50, 100 and 200 milligrams) given intramuscularly for 2 consecutive days in a group of alcoholic patients, none of whom had any clinical signs of WKS, in an alcohol detoxification center. Post-treatment, patients were compared based on their performance on a delayed alternation task test, established to be sensitive to the cognitive impairments of Wernicke-Korsakoff Syndrome. Patients who received the highest dose of thiamine showed superior performance (Ambrose *et al.*, 2001). However, the initial thiamine status of this patient group was not known. As a result of the paucity of data from randomized clinical trials, the Cochrane Collaboration concluded that currently, there is insufficient data available to provide clinical guidelines regarding the dose, frequency, route or duration of thiamine for the treatment of WKS due to alcoholism (Day *et al.*, 2004).

In various studies/clinical cases, thiamine 100 mg has been given intravenously for several days to two weeks, followed by maintenance doses of 50–100 mg orally per day until the patient is able to eat a well-balanced diet regularly (Lacasse and Lum, 2004; Chiossi *et al.*, 2006). Long-term treatment and prevention should include continued oral thiamine supplementation, alcohol abstinence and a balanced diet (Ogershok *et al.*, 2002), but this program is based on logic and overall good medical care, not data.

Following thiamine therapy in the acute state, one may obtain a dramatic response, which essentially confirms the diagnosis (Squirrell, 2004). Improvement in ophthalmoplegia is often the first sign of treatment benefit and may occur within hours (Koontz *et al.*, 2004; Doherty *et al.*, 2002). Ataxia may take days to weeks but 25% of cases may not improve at all. Residual peripheral neuropathy is also not

uncommon (Worden and Allen, 2006; Weidauer *et al.*, 2004; Chiossi *et al.*, 2006). Chiossi, in his review of WE cases due to hyperemesis gravidarum, found that only 29% of patients obtained complete resolution of symptoms, while 53% showed resolution of most signs and symptoms within three months (Chiossi *et al.*, 2006). Improvement in mental status is variable and up to 84% of patients may develop Korsakoff's psychosis (Harrison *et al.*, 2006; Morcos *et al.*, 2004; Homewood and Bond, 1999). At a two-year follow-up visit, one patient, whose oculomotor and imaging studies had shown improvement, had persistent symptoms of severe cognitive deficits, vertigo and loss of sphincter control (Attard *et al.*, 2006). Improvement of imaging studies may be seen up to four months of treatment with thiamine (Loh *et al.*, 2004). Delay in treatment may result in irreversible neuronal death and possibly death of the patient (Gui *et al.*, 2006).

Prevention

Clearly, one of the most important prevention strategies is physician and patient education in this area. In addition, there has been much debate over thiamine fortification of alcoholic beverages in order to prevent Wernicke's encephalopathy in alcoholics, the most susceptible population,. In 1987, Australia's Mental Health Committee recommended fortification of all Australian beer and flagon wine but this was never implemented. In most developed countries, bread (white flour) is enriched with thiamine to restore what is lost from the whole wheat in the process of milling. Australia adopted this plan in 1991, using the same level of enrichment as the United States (6.4 mg thiamine hydrochloride/Kg flour). The incidence of WE in the five years after the above implementation in Australia was 40% lower (perhaps fortuitously) than in the five year period prior to bread fortification. In addition, the post-mortem diagnosis of WE in Sydney, Australia has declined from 2.1% to 1.1% (Truswell, 2000).

Conclusion

There exists a great disparity between the number of patients diagnosed with WE while alive and the number of patients diagnosed post-mortem. This issue can be improved when a high index of suspicion for WE is employed for not only alcoholic patients but any patient with malnutrition or possible thiamine deficiency. Wernicke's encephalopathy should be considered in the evaluation of any patient found to have one or more of the classic complaints, including confusion, ophthalmoplegia and ataxia, especially in the setting of malnutrition. In patients with acute altered mental status or coma, it is essential to treat empirically with thiamine, which is safe and inexpensive, even prior to the availability of neuroimaging results. We cannot over-

emphasize that imaging and laboratory data should not delay treatment with thiamine, which should be based initially on clinical assessment (i.e., symptoms/signs).

Since the preparation of this manuscript, a recent paper has reported total tau protein levels in cerebrospinal fluid were elevated in acute WE, but declined at follow up. This may suggest that neuronal cell death occurs transiently in acute WE.

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