

THE NATURAL HISTORY AND PATHOPHYSIOLOGY OF WERNICKE'S ENCEPHALOPATHY AND KORSAKOFF'S PSYCHOSIS

ALLAN D. THOMSON^{1,2} and E. JANE MARSHALL^{3*}

¹Molecular Psychiatry Laboratory, Windeyer Institute of Medical Science, Department of Mental Health Sciences, Royal Free and University College London Medical School, 46 Cleveland Street, London W1T 4JF, ²Kent Institute of Medicine and Health Science, University of Kent at Canterbury and ³National Addiction Centre, Box 048, Institute of Psychiatry, Kings College London, De Crespigny Park, London SE58AF, UK

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Abstract — Aims: To identify the early clinical indications of thiamine deficiency and to understand the factors involved in the development of the amnesic state in alcohol-dependent individuals with thiamine deficiency. It is hoped that this will highlight the need for clinicians to treat alcohol-dependent patients prophylactically with parenteral thiamine and thus prevent the development of Korsakoff's Psychosis (KP). **Method:** We have reviewed the natural history and pathophysiology of Wernicke's Encephalopathy (WE) in both human and animal studies together with any contributory factors that may predispose the individual to thiamine deficiency. A further understanding of these problems is provided by recent studies into the metabolic consequences of thiamine deficiency and alcohol misuse. **Conclusions:** Where WE is due to thiamine deficiency alone (i.e. in the absence of alcohol misuse) KP rarely supervenes following thiamine replacement therapy. Successful treatment or prophylaxis of WE in alcohol dependence probably depends on a number of inter-related issues and is not simply a matter of early and adequate thiamine treatment. If sufficient alcohol-related neurotoxicity has occurred by the time of diagnosis, then this may be the more important or limiting factor with respect to the long-term outcome. This possible obstacle to complete recovery should not prevent every attempt being made to provide the patient with optimum brain thiamine replacement.

INTRODUCTION

Wernicke's encephalopathy (WE) is an acute neuropsychiatric condition due to an initially reversible biochemical brain lesion caused by overwhelming metabolic demands on brain cells that have depleted intracellular thiamine (vitamin B1). This imbalance leads to a cellular energy deficit, focal acidosis, regional increase in glutamate, and ultimately cell death. (Thomson *et al.*, 2002). In industrialized countries 90% of the cases of deficiency are associated with alcohol misuse (Thomson, 2000).

Failure to diagnose WE and institute adequate parenteral therapy results in death in 20% of patients; 75% will be left with permanent brain damage involving severe short-term memory loss [Korsakoff's Psychosis (KP)]. Because of the close relationship between WE and KP, reference is often made to the Wernicke–Korsakoff Syndrome (WKS) as if it were a single entity. Twenty five percent of patients with KP will be sufficiently affected to require long-term institutionalization. There has been a disturbing increase in KP in the UK over recent years, and such cases have increasingly been the subject of litigation (Ramayya and Jauhar, 1997; Cook *et al.*, 1998).

THE NATURAL HISTORY OF WERNICKE'S ENCEPHALOPATHY

The daily thiamine requirement for healthy individuals is related to their carbohydrate intake and is between 1 and 2 mg per day. This requirement increases with alcohol misuse and larger carbohydrate intake. Since the body stores are only between 30 and 50 mg, it might be anticipated that they would

be depleted in 4–6 weeks. Diets are rarely totally devoid of thiamine and, during the initial phases of deprivation, the deficit can be corrected by oral supplementation. However, this route of administration becomes less effective and finally inadequate as patients become more heavily involved in alcohol misuse (Thomson, 2000). Baker *et al.* (1975) confirmed that thiamine and vitamin B6 in food are poorly available to the alcoholic patient with liver disease.

Leevy *et al.* (1965) observed morbidly obese patients on a metabolic ward who were being maintained on total food and vitamin deprivation for weight reduction (Fig. 1). Their circulating vitamin levels, including thiamine, were monitored. As anticipated, after ~4 weeks the circulating thiamine level had fallen below the normal limit where it remained, despite oral thiamine administration, suggesting that the patients were developing malabsorption secondary to their malnutrition.

It was subsequently demonstrated that both alcohol and malnutrition may interfere with the absorption of thiamine hydrochloride in man (Thomson, 1969, 2000; Thomson *et al.*, 1970).

Low circulating levels of thiamine have been reported in 30–80% of alcoholic patients (Thomson *et al.*, 1987; Cook *et al.*, 1998). The incidence and the extent of depletion varies from one group to another, depending on the degree of malnutrition, liver damage, and alcohol intake.

The results obtained also depend in part on the method used to measure either the concentration of thiamine in blood or tissues or the activity of one of the enzymes requiring thiamine e.g. transketolase (Dreyfus, 1962; Pratt *et al.*, 1985). High performance liquid chromatography (HPLC) measures all four phosphorylated forms of thiamine (Fig. 2).

This technique has demonstrated that current alcohol misuse causes low circulating levels of all forms of thiamine except monophosphate compounds and that liver cirrhosis is associated with decreased thiamine diphosphate concentrations and impaired thiamine phosphorylation. (Tallaksen

*Author to whom correspondence should be addressed at: Tel.: +44 207 919 2345; Fax: +44 207 919 2349; E-mail: jane.marshall@iop.kcl.ac.uk

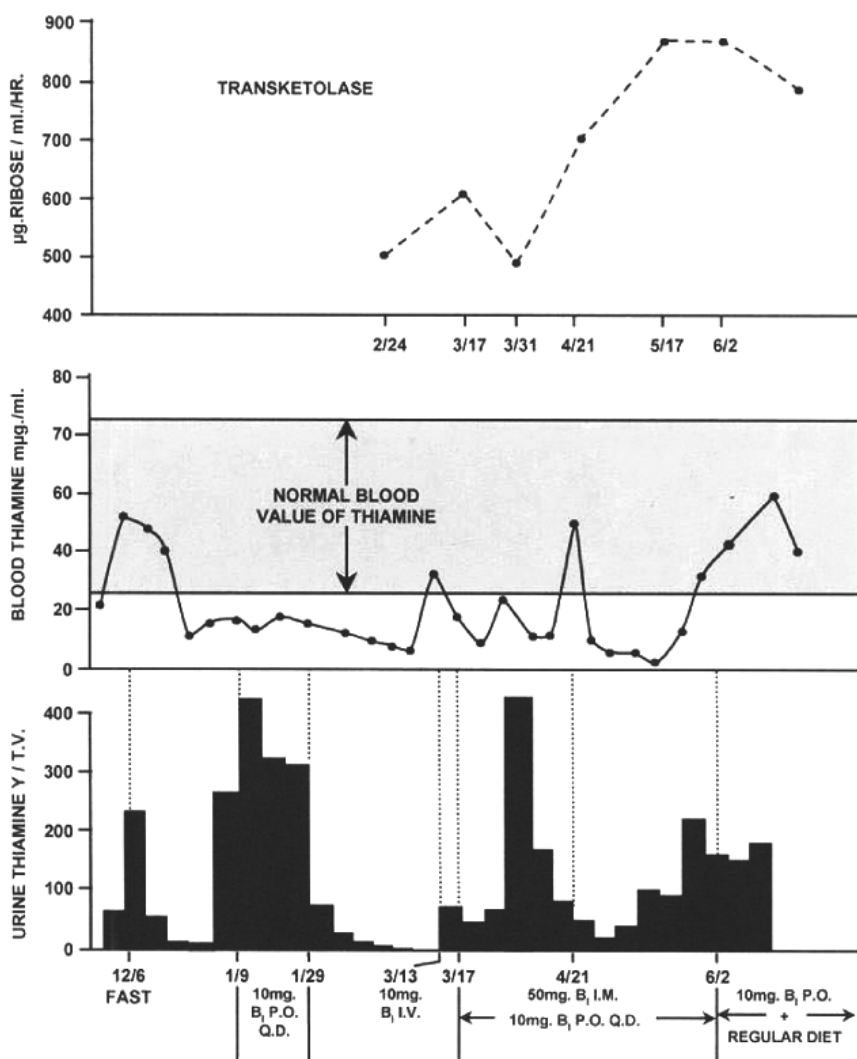


Fig. 1. Influence of vitamin and food deprivation on thiamine metabolism. [Adapted from Leevy *et al.* (1965).]

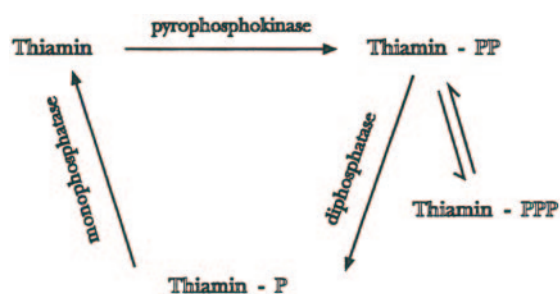


Fig. 2. The interactions of thiamine, thiamine monophosphate (thiamin-P), thiamine-diphosphate (thiamin-PP), and thiamine-triphosphate (thiamin-PPP). [From Tallaksen *et al.* (1992).] With permission.

et al., 1992, 1993a,b). More recently, Mancinelli *et al.* (2003) have described an isocratic HPLC method for the assessment of thiamine (T), thiamine monophosphate (TMP), and thiamine diphosphate (TDP) in human erythrocytes, which has advantages over previous methods and is suitable for both clinical and research purposes. They reported that the T and TDP levels were significantly lower in alcoholic patients

compared with control subjects. These studies show that as patients become more involved with excessive alcohol intake, they are increasingly at risk of developing significant thiamine deficiency. However, there is no laboratory test that will diagnose WE, although low circulating levels will indicate the patients who are at particular risk.

HOW LONG DOES IT TAKE TO DEVELOP WE?

Not all alcoholics are equally at risk of developing WE, the reasons for which may depend in part on the factors discussed below, but there is increasing evidence that there may also be a genetic predisposition to developing WE (Blass and Gibson, 1977; Hrubec and Omenn, 1981; Martin *et al.*, 1986; Heap *et al.*, 2002).

Pioneering work by Williams *et al.* (1942) studied subjects who were well nourished at the beginning of the experiment and who did not consume any alcohol during the period of observation. They were given a diet containing thiamine at 0.22 mg/1000 cal. After 89 days disturbing symptoms

necessitated giving extra thiamine in one subject, whereas the remaining nine subjects continued for 131–196 days. The symptoms were suggestive of early WE but disappeared after the administration of thiamine hydrochloride by subcutaneous injection of 1.0 mg followed by 3.0 mg orally for 7 days, thereafter 7.5 mg given p.o. daily in divided doses.

De Wardener and Lennox (1947) reviewed 52 cases of WE in a Singapore prisoner-of-war hospital. At no time was the minimum of 1 mg of thiamine attained in their diet. The first case of WE occurred after 6 weeks of captivity. WE in POWs was often precipitated by dysentery. Early symptoms consisted of loss of appetite, and then nausea and vomiting. These symptoms were often followed by giddiness and diplopia. The next symptoms included insomnia, anxiety, difficulty in concentration, loss of memory for the immediate past, and gradual decompensation consisting of confusion, confabulation, and hallucinations progressing to coma.

Recently there has been a tragic outbreak of a life-threatening thiamine deficiency in infants in Israel caused by a defective soy-based formula, which contained no detectable thiamine. The symptoms again included vomiting, lethargy, restlessness, developmental delay, ophthalmoplegia, nystagmus, and other symptoms probably related to associated infections. This report provides a dramatic example of the body's essential requirement for thiamine, especially the brain (Fattal-Valevski *et al.*, 2005). Sgouros *et al.* (2004) have evaluated a set of eight questionnaire items and found them to be predictive of thiamine deficiency in severely alcohol-dependent inpatients (Table 1).

Victor *et al.* (1989) studied 154 males and 91 females with WE (ratio 1.7:1). Their age varied from 30 to 70 years with the highest incidence in the 5th–6th decade. Alcohol misuse had usually been present for many years and was frequently associated with inadequate dietary intake over a period of months or years. However, 3 female patients gave histories of drinking for only 2, 6, and 9 months, respectively. Turner *et al.* (1989) presented a case of WE developing in a patient at the age of 18 years.

Harper (1979) studied 51 cases of WE in Australia (38 males, 13 females), aged 30–90 years, with the highest incidence in the 5th decade. Just under half (20/51) were 15 kg below their normal body weight; 14 had fatty livers; 19 cirrhosis; and 2 acute alcoholic hepatitis. Only 7/52 were diagnosed before death. It is possible that the patients may have had a chronic form of the disease, due to subclinical encephalopathy, in which normal signs may have been absent.

It is of interest that work with primates (Witt *et al.*, 1983; Witt, 1985) has shown that severe structural brain damage can be produced by one period of thiamine deprivation and that the length of a single deprivation period may be more important than the number of periods. The effects of thiamine deficiency are cumulative, in that the symptoms appear sooner with repetition of the deficiency, and the number of brain structures affected tend to increase. There is also evidence that alcohol permanently damages the thiamine-depleted brain to a greater degree than thiamine depletion alone (Price *et al.*, 1993; Ciccia and Langlais, 2000; Crowe and El-Hadj, 2002).

Table 1. Questions, symptoms, and signs to help identify patients at risk of thiamine deficiency and/or neurotoxic damage

Signs and symptoms of thiamine deficiency [DeWardener and Lennox (1947); Thomson *et al.* (1980)]

Loss of appetite
Nausea and vomiting
Fatigue, weakness, apathy
Giddiness and diplopia
Insomnia, anxiety, difficulty in concentration
Loss memory for immediate past
Decompensation: confusion, disorientation, confabulation, hallucinations
Coma

Thiamine deficiency questionnaire [Sgouros *et al.* (2004)]

Frequency of eating carbohydrate daily as (i) fruit and vegetable (ii) meat, fish or poultry (iii) in the past year
Frequency of meal completion
Weight loss in past year (in kg)
Frequency of missed meals because of lack of funds (per week)
Frequency of reduced appetite with avoidance of meal (per month)
Total number of episodes of vomiting in past month
Co-occurrence of other nutritionally related conditions (polyneuropathy, amblyopia, pellagra, amaemia or subacute combined degeneration): yes or no

Body mass index

General clinical impression of nutritional status

Factors predisposing to neurotoxicity

Genetic predisposition to alcohol dependence and neurotoxic effects of alcohol (40–60% of the variance for vulnerability in alcohol use disorders is genetic; this includes vulnerability for genetic–environmental interaction)
Quantity/frequency of alcohol use (units of alcohol on a typical drinking day; units of alcohol per drinking occasion; frequency of drinking occasions; frequency of having 6 units or more on one occasion)
Severity of dependence: frequency of early morning drinking to relieve withdrawal symptoms is a useful clinical measure of severity of dependence
Acute intoxication (direct neurotoxic effect, alteration in receptors and neurotransmitters, ion channels)
Withdrawal syndromes, including withdrawal seizures and delirium tremens
Concurrent drug use, particularly cocaine [alcohol and cocaine taken together are metabolised to a neurotoxic metabolite, cocaethylene [McCance-Katz *et al.* (1998)]]
Frequency of occurrence of 'memory blackouts' (defined as transient circumscribed memory deficit episodes that occur during episodes of severe intoxication; related to peak alcohol concentration)
Alcohol-related liver damage: Alcohol-dependent males with liver cirrhosis shown to have more brain tissue loss than alcohol-dependent males without cirrhosis [Harper *et al.* (1995)]

CONTRIBUTORY FACTORS

Many factors will interact to reduce the supply of thiamine to specific groups of brain cells and to determine whether the available thiamine can be utilized so that it becomes extremely difficult for us to predict, except in very general terms, who will develop WE. It is also known that recurrent brain damage may occur without the patient presenting to the medical profession. It is important to understand how this occurs and whether it predisposes the individual to further damage. Clearly genetic factors are important but we do not yet know what this means at a biochemical level (Thomson *et al.*, 2002).

Primary thiamine deficiency results from inadequate thiamine intake and general malnutrition and is seen in a number of conditions not related to alcohol misuse (Thomson *et al.*, 2002). Secondary thiamine deficiency, caused by alcohol misuse, starts with a group of individuals some of whom will be genetically predisposed to brain damage. As the alcohol misuse continues, complications will occur that limit the supply of thiamine, which may already be at dangerously low levels. For example, it has been shown that malnutrition can interfere with thiamine absorption, which in man requires an active transport system (Thomson *et al.*, 1970), but further work is required to determine when this becomes a significant and perhaps a critical problem. Independently of the problems caused by general malnutrition, deficiency of folic acid (Thomson *et al.*, 1971, 1972) and thiamine depletion itself can cause malabsorption of thiamine from the gastrointestinal tract.

Ethanol can cause damage to the intestinal mucosa, in which case thiamine absorption can be reduced by up to 90% (Thomson *et al.*, 1970; Gastaldi *et al.*, 1989). Recently Reidling *et al.* (2002) investigated an intestinal thiamine transport mechanism, THTR-1 (SLC19A2), which is an active sodium independent transport system, driven by the normal pH gradient across the membrane (Dudeja *et al.*, 2001; Reidling *et al.*, 2002). The SLC19 gene family plays an important role in the transport and homeostasis of folate and thiamine in the body. SLC19A1 has been shown to transport monophosphate and pyrophosphate derivatives of thiamine. The SLC19A2 is a high affinity transporter gene, while the SLC19A3 (THTR-2) controls thiamine transport at a lower affinity. Reidling and Said (2005) have recently demonstrated that both intestinal and renal thiamine uptake processes are adaptively upregulated during thiamine deficiency. This mechanism may malfunction in patients who develop WE, or fail in the continuing face of lack of thiamine, or be damaged by the products of ethanol metabolism.

It is possible that subtle genetic alterations in the transporter protein may lead to diminished capability to transport thiamine into brain cells. In order for dietary thiamine to become active in brain cell metabolism, it must undergo at least four transport steps. Initially this involves two transport steps to reach the blood, the first being uptake by the brush border membrane, followed by export out of the enterocyte by the basolateral membrane. Thiamine is then transported by the blood to the liver, heart, and other tissues except neuronal tissue. Thiamine must be transported into the CSF, via the blood-brain barrier, in order to reach the neurons. Once within the

neuronal cell, thiamine must be further transported into the mitochondria and nucleus.

Variations in the effectiveness of the various transport systems, and the subsequent phosphorylation required to become the co-enzyme, may contribute to how well an individual copes with thiamine deficiency or responds to therapy (Singleton and Martin, 2001). Recent investigations have begun to identify such changes (Guerrini *et al.*, 2003, 2004, 2005) but more work is required to determine their significance.

The supply of thiamine to the body can be reduced by chronic diarrhoea or persistent vomiting (Price *et al.*, 1993; Rotman *et al.*, 1994; Ohkoshi *et al.*, 1994). Hepatic disease reduces storage and interferes with thiamine metabolism. Ethanol accelerates cerebellar metabolism of thiamine (LaForenza *et al.*, 1990), inhibits thiamine pyrophosphokinase, and the renal tubular reabsorption of filtered thiamine is exacerbated by furosamide therapy (Hoffman and Goldfrank, 1989). Magnesium is required as a cofactor for many thiamine dependent enzymes and deficiency of this metal may also induce clinical signs of thiamine deficiency (Traviesa, 1974). A number of other disorders may affect thiamine bioavailability or metabolism, including gastrointestinal carcinoma, AIDS, anorexia and anorexia nervosa, multiple organ failure, and rapid parenteral carbohydrate loading (Thomson *et al.*, 2002).

Patients who develop WE in association with alcohol misuse require much larger parenteral doses of thiamine, up to 1 g in 24 h, if they are to be treated successfully (Cook *et al.*, 1998). This presumably is related to the above facts and to the damage caused to the enzymes by the products of alcohol metabolism (Pratt *et al.*, 1985).

DEVELOPMENT OF THE AMNESIC STATE

The development of KP, characterized by well-recognized amnesic defects, with all of its devastating consequences for the patient, is an indication that treatment has failed. Individuals with non-alcoholic Wernicke's not only require less thiamine, but the condition rarely develops into KP. This may be because non-alcoholic patients may present at an earlier stage of WE, may have more obvious symptoms, and may engender a more active treatment response (Homewood and Bond, 1999).

Amnesic defects have been shown to be present in 56–84% of some groups of patients, treated for WE with parenteral thiamine, and followed-up for up to 2 years (Victor *et al.*, 1971; Wood *et al.*, 1986). This may be because the doses of thiamine given at the time were much smaller (100–250 mg i.m. or i.v. daily) than those currently recommended for treatment of WE (Cook *et al.*, 1998; Thomson *et al.*, 2002). Blood-brain barrier disruption has been demonstrated using MRI scanning during acute WE, suggesting that high blood to brain concentrations of thiamine may be required (Schroth *et al.*, 1991). Recent work by Kruse *et al.* (2004) indicates that inhibition of the α -ketoglutarate dehydrogenase complex (α -KGDH) causes a change in mitochondrial function, and sets in motion a cascade of abnormalities, leading to oxidative stress. This leads to the production of nitric oxide from

vascular endothelial cells that may be responsible for the distribution of brain lesions in WE.

Equally the degree of permanent brain damage at the time that the patient presents may vary, or defects induced by thiamine deficiency may become irreversible if the ethanol has caused sufficient associated neurotoxicity. Experiments in chicks exposed to both thiamine deficiency and ethanol have shown development of memory impairment that is irreversible following thiamine replacement. In contrast, the memory of chicks exposed to thiamine deficiency alone will return to normal following correction of thiamine deficiency. This suggests the importance of neurotoxicity in the evolution of alcohol-related brain damage in the context of thiamine deficiency (Crowe and El-Hadj, 2002).

At present, the only parenteral high potency B-complex vitamin therapy available in the UK is Pabrinex. This contains riboflavin and pyridoxine, which theoretically may limit the accumulation of glutamate in the presence of thiamine deficiency (Thomson *et al.*, 2002), and also nicotinamide, which may correct unsuspected nicotinic acid deficiency. It is possible that these additional ingredients might help prevent the development of KP, although controlled trials have not yet been performed.

The recent Cochrane review (Day *et al.*, 2004) agrees with Cook *et al.* (1998) that there is insufficient evidence from randomized controlled trials to guide the clinician as to the optimum dose, frequency, route, or duration of thiamine treatment for prophylaxis or the treatment of WE. Although the abnormal eye movements, ataxia, and global confusion appear to improve relatively rapidly, impairments in memory and learning respond more slowly or incompletely, suggesting that they may be due to a different mechanism(s), which may involve interactions between the metabolic effects of thiamine deficiency and the neurotoxic contribution from alcohol.

Numerous mechanisms have been suggested to explain the selective loss of neurons found in thiamine deficiency, in the hope that they may lead to more effective therapy for WE. They include cerebral energy dysfunction (Aikawa *et al.*, 1984; Thomson *et al.*, 2002); breakdown of the blood-brain barrier referred to above (Calingasan *et al.*, 1995a; Harata and Iwasaki, 1995); altered glutamate neurotransmission caused by extracellular glutamate and its impaired transport function, discussed below (Hazell *et al.*, 1993, 2001); together with *N*-methyl-D-aspartate (NMDA) receptor-mediated excitotoxicity (Langlais and Mair, 1990); the accumulation of amyloid precursor-like protein (Calingasan *et al.*, 1995b); increased free radical production (Langlais *et al.*, 1997); increased expression of superoxide dismutase (Todd and Butterworth, 1997) consequent to increased microglial response (Todd and Butterworth, 1999); induction of nitric oxide (Calingasan *et al.*, 1998); and oxidative stress (Langlais *et al.*, 1997; Desjardins and Butterworth, 2003). For further discussion please see Kruse *et al.* (2004). It is difficult to know which of the changes are of primary importance and it may be that multiple genetic defects and the combined effects of a number of processes may be responsible. Equally, multiple episodes of alcohol withdrawal may predispose the individual to permanent damage in the future.

RELEVANCE OF THE NMDA IONOPHORE CHANNEL COMPLEX

Hazell *et al.* (1993) and Langlais and Mair (1990) have suggested that the NMDA channel complex may be implicated in thiamine deficiency and neuronal death. This can be summarized as follows:

- (i) Chronic alcohol exposure blocks the NMDA receptor at the glutamate site, causing an increase in glutamate receptors (up-regulation).
- (ii) Cessation of alcohol frees the receptors to accept more glutamate, causing a hyperactive state.
- (iii) Thiamine deficiency causes an increase in glutamate concentration.
- (iv) The severity of the withdrawal may in part be determined by the degree of thiamine deficiency, made worse by accompanying B2 and B6 deficiency [gamma-aminobutyrate (GABA) shunt].
- (v) Administered thiamine acts to reduce the raised glutamate levels and so limit the excitotoxicity.
- (vi) Patients with WE due to thiamine deficiency alone do not have upregulated receptors. It is conceivable that this is the critical factor determining the degree of recovery possible.

The clear message is that patients (or individuals) at risk must be treated before they become thiamine deficient, in order to prevent the occurrence of this pernicious neurotoxicity. This is another reason why heavy drinkers are at increased risk: they are 'primed' for injury to occur as soon as brain thiamine reaches a critically low level!

Preliminary trials of the drug Memantine (NMDA antagonist) have proved effective in treating patients with WE (Rustembegovic *et al.*, 2003). Reports that pre-treatment of thiamine deficient animals with the competitive NMDA receptor antagonist MK801 was neuroprotective were subsequently found to be largely due to the drug's anticonvulsant properties. Increases in extracellular brain glutamate in thiamine deficiency are probably due to a selective downregulation of astrocytic glutamate transporters, which could be due to reactive oxygen species and nitric oxide (Butterworth, 2003).

Changes in a number of CNS neurotransmitter systems have been reported in thiamine deficiency, suggesting that thiamine is important for normal neurotransmitter function. Acetylcholine, GABA, glutamate, and aspartate are produced primarily through the oxidative metabolism of glucose (Haas, 1998). In particular changes are seen in 5-HT mechanisms. In thiamine-deficient monkeys exhibiting a pattern of memory loss similar to patients with WE, it was proposed that their amnesia was caused by a loss of 5-HT containing neurons. The associated ataxia and thermoregulatory changes accompanying thiamine deficiency were thought to be due to 5-HT neurotransmitter changes. CSF levels of 5-HIAA were reduced in patients with WKS (Haas, 1998). Recent work suggests that thiamine may inhibit 3H-serotonin uptake (Keating *et al.*, 2004) providing further evidence that thiamine may be acting as a neurotransmitter or modulating agent, as well as a co-factor in brain metabolism, and that its deficiency may be associated with adverse mood changes and detrimental behaviour (Bonner *et al.*, 2004). These behavioural changes could, in turn, lead indirectly to increased alcohol consumption.

This emphasizes the importance of treating thiamine deficiency early and adequately.

Cochrane *et al.* (2005) have reported treating three patients with WKS with the acetylcholinesterase inhibitor, donepezil, for 6–8 months. The encouraging results show that further studies are indicated.

CONCLUSION

Thiamine deficiency develops over a period of months, with damage in the Wernicke area often following an increased demand for thiamine, for instance during alcohol withdrawal or DTs. Recurrent 'subclinical' episodes of damage may not be diagnosed because the patient does not present to an experienced healthcare professional, or they are missed clinically. The classic triad of signs cannot be relied upon to accompany all lesions, and successful treatment relies on early adequate treatment or prevention.

There are well-documented cases from the scientific literature identifying the early signs and symptoms of thiamine deficiency and providing us with a time course of events (Table 1). These should allow the clinician, who is clinically aware of the possibility of WE, to treat the patient prophylactically, and to prevent the development of KP, providing that the patient presents at this stage of the illness. However, many symptoms of thiamine deficiency are non-specific and have been attributed to alcohol misuse itself.

There are many contributory factors that will combine to restrict the supply of thiamine to the brain and the clinician should be aware of these when assessing the patient. Recent evidence suggests that some patients may be genetically predisposed to developing WE and this sub-group may experience the consequences of thiamine deficiency earlier than the general population as a result of impaired thiamine transport or associated damage by ethanol. At present we have no test that will identify these patients and the clinician must rely on careful observation and assessment.

It is essential to try to limit the neurotoxicity that probably occurs as a result of thiamine deficiency and ethanol metabolism and will accompany recurrent alcohol withdrawal episodes.

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