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COMMENTARY

Time to Act on the Inadequate Management of Wernicke's Encephalopathy in the UK

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Abstract — Wernicke's encephalopathy (WE) is a serious medical emergency whose pathogenesis is well understood and reviewed in this paper. Summarizing the evidence for its prophylaxis and management, the authors suggest that, in the UK, there is evidence that many patients identified as being at risk of WE currently do not receive appropriate treatment, despite the availability (not universal) of guidelines and protocols.

See related paper in this Issue: Rees E & Gowing LR (2013) Supplementary thiamine is still important in alcohol dependence. *Alcohol Alcohol* **48**: 88–92.

Wernicke's encephalopathy (WE) is the acute phase of a potentially fatal disorder resulting from thiamine (vitamin B_1) deficiency (Harper *et al*., 1986; Thomson *et al*., 2002). If left untreated, WE can have serious neurological consequences that can lead to long-term institutionalization or even death (Thomson *et al*., 2002). WE is medical emergency (Thomson *et al*., 2009) that is reversible with timely administration of appropriate treatment (Thomson *et al*., 2002). We review current knowledge on WE and its management and highlight shortcomings in the current management of WE in the UK, discussing possible changes that could improve diagnosis and outcomes.

CAUSES OF WE

The underlying cause of WE is an inadequate supply of thiamine to the brain. Thiamine deficiency can result from a number of conditions, including poor nutrition (inadequate intake of thiamine), medical conditions associated with excessive loss of thiamine and impaired intestinal absorption of thiamine. It is often associated with alcohol misuse (Thomson *et al*., 2002; Rees and Gowing, 2013).

Chronic alcohol misuse is the most common cause of WE in the Western world. Studies have confirmed that circulating levels of thiamine are reduced in 30–80% of alcohol misusers (Thomson *et al*., 2009). Chronic alcohol misusers are at particular risk of developing WE because:

- They are more likely to have a lower level of self-care and a poor diet (Thomson *et al*., 2002).
- Absorption of thiamine is reduced by both alcohol and malnutrition acting separately or together (Cook *et al*., 1998).
- They have increased metabolic demands in relation to glucose utilization and alcohol metabolism (Cook *et al*., 1998; Sechi and Serra, 2007).
- They have reduced hepatic storage of thiamine (Cook *et al*., 1998).
- Ethanol neurotoxicity causes impaired utilization of thiamine (Sechi and Serra, 2007).

Malnutrition unrelated to alcohol misuse is another important cause of WE (Thomson *et al*., 2002). It was recently estimated that, at any given time, there are >3 million people in the UK who are either malnourished or at risk of malnourishment. A vast majority of these (93%) are living in the community, including 2–3% of whom are in sheltered housing, 5% in care homes and 2% in hospital [British Association for Parenteral and Enteral Nutrition (BAPEN), 2009]. The number of malnourished people leaving NHS hospitals in England has risen by 85% over the past 10 years. Recently, the UK government admitted that, in 2006–2007, nearly 140,000 patients left hospital suffering from malnourishment (House of Commons debate, 2008). Hospitals are either unaware of the degree of malnutrition or fail to correct the deficits required to repair the damage caused by alcohol misuse and required for normal brain function.

PATHOPHYSIOLOGY OF WE

Certain areas of the brain are characterized by high thiamine content and turnover, and these areas are most vulnerable to the depletion of thiamine (Sechi and Serra, 2007). Typical histopathological changes occur in specific areas of the brain (Sechi and Serra, 2007):

- 100% of WE patients show changes in the medial dorsal thalamic nucleus.
- In 50% of patients, there are changes in the periaqueductal grey, mammillary bodies and medial thalamus.
- In a third of cases, the superior vermis of the cerebellum is affected.

Thiamine diphosphate acts as a co-factor for a number of thiamine-dependent enzymes. Thiamine deficiency reduces the activity of these enzymes and this leads to alterations in mitochondrial activity, impairment of oxidative metabolism and decreased energy status eventually leading to selective neuronal death (Hazell and Butterworth, 2009).

Initially, the pathophysiological changes inherent to WE are reversible with administration of parenteral thiamine as long as necrosis has not occurred. Without adequate treatment, the changes become irreversible (Sechi and Serra, 2007).

THE IMPACT OF WE

Once lesions become unresponsive to parenteral thiamine, they can result in permanent neurological sequelae [Korsakoff's psychosis (KP)] or death. KP is characterized by amnesia, disorientation and confabulation (Sechi and Serra, 2007). Owing to the close relationship between WE and KP, the disorder is often referred to as the Wernicke–Korsakoff syndrome (WKS) (Thomson *et al*., 2002).

The international prevalence of WKS ranges from 0 to 2.8% (UK, 0.5%; mainland Europe, 0.1–1.3%; USA, 0–1%; Australia, 2.1–2.8%) (Harper *et al*., 1995). While recent data for the full economic costings of WE are unavailable, in 1977 it was estimated that the institutionalization of eight WE patients per million in the USA would cost $70 million annually. Extrapolating these figures to the present indicates that WE is extremely burdensome in health economic terms (Thomson *et al*., 2006a). Without treatment, patients with WE are likely to develop KP that could require long-term, if not life-long, care (Thomson *et al*., 2002).

PRESENTATION OF ALCOHOL MISUSERS/ DEPENDENT DRINKERS TO THE HEALTH CARE SYSTEM

Chronic alcohol misusers may present acutely to hospital in a state of intoxication/withdrawal, which can mask the confusion and ataxia of an underlying WE episode. These patients may also be abusive to staff (Thomson *et al*., 2002), which can result in failure to offer the attention and treatment needed.

A number of conditions may coexist with alcohol misuse disorders, and these co-morbidities can increase the risk of developing WE. These may sometimes be obvious during the initial examination (Thomson *et al*., 2009).

- Diabetic ketoacidosis
- Chronic renal failure
- Severe obesity
- Ulcerative colitis
- Pernicious anaemia
- Anorexia nervosa
- Patients with Alzheimer's disease
- Neglect in old age, especially if living alone
- Chronic schizophrenia
- Widespread tuberculosis
- AIDS
- Teenage pregnancy with poor nutrition/drug misuse while mother still growing
- Patients with protracted vomiting, including during pregnancy
- Sepsis

There is no simple blood test to detect WE. However, over the years a number of clinical signs have been reported that identify patients with WE, most notably (Thomson *et al*., 2009):

- oculomotor abnormalities,
- cerebellar dysfunction (ataxia) and
- confusion.

Together, these three signs have been termed the 'classic triad' and have been used as a diagnostic indicator of WE. However, they have poor sensitivity in detecting WE, with only 16.5% of patients exhibiting all three signs (Figure 1) (Harper *et al*., 1986). It is therefore likely that WE has been under-diagnosed, in part due to the poor sensitivity of the 'classic triad' (Harper *et al*., 1986; Thomson *et al*., 2009). The consequences of inadequate treatment of WE are significant and it may be fatal in up to 20% of patients (Thomson *et al*., 2002).

Early signs and symptoms of thiamine deficiency have been identified, and these occur whether the patients are alcohol misusers or have thiamine deficiency alone (Table 1). Patients who exhibit these early signs should be offered prophylactic thiamine. Patients with a presumptive or actual diagnosis of WE will require larger parenteral doses of thiamine and more prolonged treatment (Thomson *et al*., 2009). The most common clinical sign in patients with WE

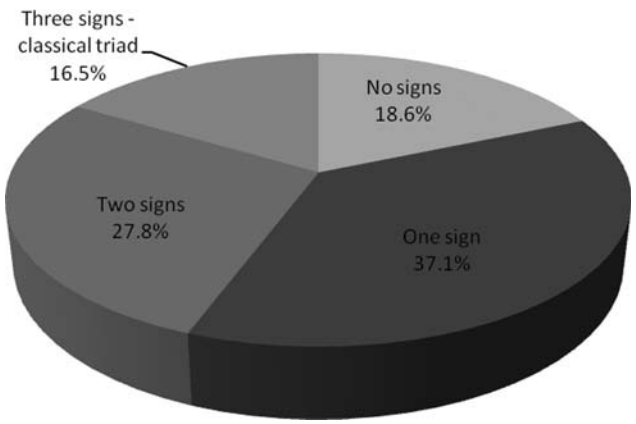

Fig. 1. Diagrammatic representation of the incidence of clinical signs of WKS. Adapted from Harper *et al*. (1986).

Table 1. Signs and symptoms relevant to clinical evaluation of thiamine deficiency[a]

Clinical history
• Weight loss in past year
• Reduced body mass index
• General clinical impression of patient's nutritional status
• High dietary carbohydrate intake
• Recurrent episodes of vomiting in the past month
• Co-occurrence of other nutritionally related conditions (polyneuropathy, amblyopia, pellagra, anaemia)
Early signs and symptoms of thiamine deficiency
• Loss of appetite
• Nausea/vomiting
• Fatigue, weakness, apathy
• Giddiness, diplopia
• Insomnia, anxiety, difficulty in concentration
• Memory loss
Later signs and symptoms
• Classic triad: oculomotor abnormalities, cerebellar dysfunction (ataxia) and confusion
• Quiet global confusion with disorientation in time/place
• Confabulation/hallucination
• Onset of coma

Adapted from Thomson *et al*. (2009). Reproduced with permission from Practical Gastroenterology, June 2009.
[a]Patients may present with different combinations of symptoms and signs.

relates to abnormalities of higher mental function and level of consciousness. However, these are relatively 'soft' clinical signs compared with ataxia or oculomotor abnormalities (Harper *et al*., 1986). It is, therefore, essential to have a high index of suspicion of WE when treating chronic alcohol misusers, to avert these potentially devastating consequences (Harper *et al*., 1986).

MANAGEMENT OF WE

Thiamine blood levels do not reflect brain levels of thiamine diphosphate, neither do they predict the development of WE in an individual. As there is no defined circulating thiamine level at which WE develops in all patients, at best it may indicate those at risk (Thomson *et al*., 2009). There are no specific routine laboratory tests available to measure thiamine deficiency; therefore, WE remains a clinical diagnosis (Sechi and Serra, 2007).

Prompt thiamine supplementation is required in WE or suspected WE and delaying treatment may increase the likelihood of morbidity or mortality (Sechi and Serra, 2007; Thomson *et al*., 2009; 2012). In patients who develop WE in association with alcohol misuse, rapid correction of thiamine deficiency requires a high plasma concentration to cross the blood–brain barrier, and can only be achieved by parenteral therapy (Thomson *et al*., 2002). Parenteral thiamine therapy is prescribed in the UK in the form of Pabrinex and should be given before glucose supplementation. The Royal College of Physicians recommend at least 3 days of treatment with IV thiamine (Thomson *et al*., 2009, 2002), but treatment should be given for as long as improvement is observed. Recently, NICE have published their recommendations for the treatment of WE, which are largely in agreement with previously published guidelines and are discussed below. Pabrinex also contains nicotinamide which reverses brain changes resulting from a lack of this vitamin, as well as vitamin B_6, vitamin C and vitamin B_2 (Cook *et al*., 1998; Thomson *et al*., 2006b, 2002). It is possible that these additional ingredients may help to prevent KP although controlled trials concerning this have not been performed (Thomson *et al*., 2006b). The immediate treatment of acute WE is as follows (Thomson *et al*., 2009; British National Formulary, 2010; National Institute for Health and Clinical Excellence, 2010):

- IV thiamine: two to three pairs of Pabrinex ampoules every 8 h for 5 days,
- multivitamins IV,
- correct magnesium deficiency: average deficit 2 meg/kg: check renal impairment,
- correct fluid and electrolyte losses and
- thiamine must always be given before a glucose load.

It must be emphasized that the brain depends on a number of vitamins, minerals and fatty acids for normal function. Patients with thiamine deficiency will frequently have a number of other deficiencies, and it is essential that these should also be remedied as part of treatment. Thiamine-dependent enzymes cannot operate in a magnesium-deficient state. This means that treating patients with thiamine without addressing a magnesium deficiency will lead to exacerbation of the WE (Thomson *et al*., 2009).

Patients with WE due to dietary deficiency alone will usually respond to smaller and often oral doses of thiamine (Thomson *et al*., 2009). High concentrations of circulating thiamine will presumably be required until the damage to thiamine transport systems and apoenzymes, caused by the combination of thiamine deficiency and alcohol metabolism, have been repaired.

Any malnourished chronic alcohol misuser is at high risk of WE (Sechi and Serra, 2007), and should be considered a candidate for parenteral thiamine, as for patients who have a clinical diagnosis of WE. In patients with evidence of chronic alcohol misuse, particularly those with a poor diet, treatment with parenteral thiamine and nutritional supplementation should begin without delay (Thomson *et al*., 2009, 2002).

INVESTIGATING MANAGEMENT OF WE IN THE UK

Recent audits (2005 or later) on the management of WE in the UK show variation in diagnosis and standards of treatment for patients with suspected or clinically diagnosed WE.

These audits show variation in the dose and duration of thiamine supplementation (see Table 2):

- not all patients for whom WE treatment is indicated receive thiamine supplementation;
- doctors are often unaware of local protocols, and do not always follow protocols correctly, even when they are readily available and
- there is a risk that patients are being under-treated.

THE EFFECT OF HOSPITAL GUIDELINES AND PROTOCOLS

Ward *et al*. (2009) found that only 60% of acute hospitals in the UK have protocols in place to manage acute alcohol withdrawal and that the majority favoured a dosing regimen different from the manufacturers' recommended dose of Pabrinex. (As there are no formal dose-ranging, placebo controlled trials, it is debatable whether recommending alternative dosing regimens can be supported.)

Littlewood *et al*. (2008) found that, of doctors working in emergency departments in Scotland, 55 of the 58 who responded to the survey (95%) were unaware of their local hospital policy.

Day *et al*. (2010) identified acute medical admissions to a hospital in Birmingham who were prescribed thiamine over a 6-month period, and clinical data from 144 case notes were obtained retrospectively. Prescribers were then provided with a flowchart summarizing the prescribing guidelines for thiamine, and prescribing patterns were re-audited 6 months later. Half of the patients had symptoms suggestive of WE recorded in their case notes and another 30% were at high risk. Prescribing guidelines were adhered to in 14% of cases, and the pharmacy-led intervention was associated with a small but significant increase in the number of patients receiving adequate treatment for WE.

Although these audits indicate that formulary prescribing guidelines and protocols are not always followed, the

Table 2. Audit findings relating to treatment and dose of parenteral thiamine

Author (year)	Study	Patients eligible for IV thiamine but not prescribed (%)	Prescribed incorrect dose (%)	Incorrect duration (%)
Collins (2005)	Audit of prescribing of IV Pabrinex in medical wards: $n = 53$ medical admissions No signs of WE: 11 Signs of WE: 26 At risk of WE: 16	—	Signs of WE: 13 (50%) At risk of WE: 16 (100%) Overall: 69%	57% of eligible patients
Johnston (2007)	$n = 52$ medical admissions with alcohol-related conditions 18 of 52 patients prescribed IV Pabrinex	61% (11/18)[a] 11 of the 18 prescribed Pabrinex did not receive it	—	—
Day *et al*. (2010)	Pharmacy-based audit in an acute medical setting (two stages) $n = 229$ medical admissions		Symptoms suggestive of WE: 50% Clinical features suggesting at risk of WE: 30%	3% received optimum dose of thiamine One third received parenteral thiamine as recommended in guidelines
Scottish Emergency Department Alcohol Audit (SEDAA) Group (2008)	Fifteen Emergency Departments in Scotland 985 attendances with serious alcohol problems		Recommended dose of parenteral B vitamins administered to 44% of ED-based treatments[b]	—
McIntosh *et al*. (2005)	Patients undergoing alcohol detoxification on general medical wards Case note audit n= 70 'pre-intervention' (parenteral thiamine indicated in 17 (24%)) $n = 93$ 'post-intervention' [parenteral thiamine indicated in 28 (28%)]	Pre-intervention 75% Post-intervention 40% Intervention: Information from the hospital guideline on the treatment of WKS was integrated into alcohol detox sheet Guidance improved adherence to guideline		
Ward *et al*. (2009)	Web-based study of acute hospital sites in UK: $n = 104$ Treatment of neuro-psychiatric syndromes or a presumptive diagnosis of neuropsychiatric syndromes in hospitals with an alcohol admission protocol	Sixty-two hospitals had protocols 42 hospital did not have protocols	73% of hospitals with protocols 62% of hospital without protocols	17%

The definitions of 'incorrect dose' and 'incorrect duration' were taken from the local protocols, which were derived from the BNF, as NICE guidance was not available at the time.
[a]Percentage of patients prescribed IV thiamine who did not receive it.
[b]44% of an appropriate and eligible group of attendances.

provision of printed guidance can lead to significant improvements in appropriate prescribing. Thus, evaluating the integration of the hospital guideline on WKS into the hospital detoxification sheet at the Royal Edinburgh Hospital, McIntosh *et al*. (2005) showed an increase in the number of eligible patients receiving appropriate treatment.

These data suggest that there remains room for improvement in the management of WE in the UK. It is important that printed guidelines, including guidance on identifying patients, are used and the correct dosing of parenteral thiamine is given to this vulnerable group of patients. All appropriate health care professionals must be trained to have a high index of suspicion in relation to WE and know the importance of prompt therapeutic intervention, and be made aware of hospital policy pertaining thereto. Audits should be performed to check that guidelines are implemented.

CONCLUSION

Local guidelines on the prevention, detection and management of WE should be clear, available and audited. Recording systems should be visible so that everyone involved in the care of the patient is apprised of treatment needs and administration. At present, in the UK, reports indicate that some patients identified as being at risk of WE do not receive adequate or appropriate treatment; therefore, some patients may develop brain damage that could have been prevented. Hospitals failing to provide adequate treatment for WE may be vulnerable to negligence actions by affected patients or their relatives.

The NICE guidelines are helpful and concur with our recommendations with one exception. We believe that there are likely to be malnourished patients in the community at risk of developing WE, but for whom there will be no available hospital beds (they may even refuse to be admitted). This was acknowledged in NICE Clinical Guideline 115 [(National Institute for Health and Clinical Excellence (NICE), 2011], but lack of evidence prevented a clear endorsement by the Guideline Development Group. However, we believe that some of these patients, not hospitalized, require parenteral thiamine to prevent brain damage.

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