Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management

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Wernicke's encephalopathy is an acute neuropsychiatric syndrome resulting from thiamine deficiency, which is associated with significant morbidity and mortality. According to autopsy-based studies, the disorder is still greatly underdiagnosed in both adults and children. In this review, we provide an update on the factors and clinical settings that predispose to Wernicke's encephalopathy, and discuss the most recent insights into epidemiology, pathophysiology, genetics, diagnosis, and treatment. To facilitate the diagnosis, we classify the common and rare symptoms at presentation and the late-stage symptoms. We emphasise the optimum dose of parenteral thiamine required for prophylaxis and treatment of Wernicke's encephalopathy and prevention of Korsakoff's syndrome associated with alcohol misuse. A systematic approach helps to ensure that patients receive a prompt diagnosis and adequate treatment.

Introduction

Wernicke's encephalopathy is an acute, neuropsychiatric syndrome that is common relative to other neurological disorders. It is characterised by nystagmus and ophthalmoplegia, mental-status changes, and unsteadiness of stance and gait—although this triad is seen in only 16% of patients.[1,2] The disorder results from a deficiency in vitamin B1 (thiamine), which in its biologically active form, thiamine pyrophosphate, is an essential coenzyme in several biochemical pathways in the brain.[3] Carl Wernicke described this distinctive entity in 1881 as acute superior haemorrhagic polioencephalitis in two alcohol-misusing men and a young woman who developed persistent vomiting due to pyloric stenosis after the ingestion of sulphuric acid.[4] The classic triad and fundoscopic changes, consisting of swelling of the optic disks and retinal haemorrhages, were present in these patients.[4] All of them died within 2 weeks of onset of neurological manifestations.

Campbell and Russell in the 1940s stressed the nutritional association of the encephalopathy and suggested thiamine deficiency as a causative factor.[5] Thiamine requirement is directly related to both total caloric intake and the proportion of calories provided as carbohydrates.[6] Thus, high caloric and high carbohydrate diets increase the demand for thiamine. The recommended dose of thiamine for an average, healthy adult is 1·4 mg per day or 0·5 mg of thiamine per 1000 kcal consumed. This dose is higher in children, in critically ill conditions, and during pregnancy and lactation.[7] Because thiamine is absorbed in the duodenum by a rate-limited process, in healthy individuals, the calculated maximum amount of thiamine that can be absorbed from a single oral dose is about 4·5 mg.[8] At the blood–brain barrier, transport occurs by both passive and active mechanisms,[8] which allows a rapid correction of brain thiamine deficiency, mainly by passive diffusion, if a steep concentration gradient between plasma and the brain is established, as happens after parenteral administration of the vitamin.[8]

Although in recent years there has been an increase in the number of clinical settings in which Wernicke's encephalopathy is encountered, this potentially fatal disease is still greatly underdiagnosed in both adults and children. However, major advances have been made in our understanding of the pathophysiology, genetics, prophylaxis, and management of Wernicke's encephalopathy. In this review, we provide an update on these advances, emphasising the predisposing factors, including clinical settings, in which Wernicke's encephalopathy is encountered and offer some new insights into diagnostic and management procedures.

Epidemiology

In adults, autopsy studies have revealed a higher prevalence of Wernicke's encephalopathy lesions (0·8–2·8%) than is predicted by clinical studies (0·04–0·13%).[2,9,10] Similar data have been reported in children.[10] In particular, in adult patients who misused alcohol[2] and those with AIDS,[11] Wernicke's encephalopathy confirmed at autopsy had been missed by routine clinical examination in 75–80% of cases. In children, about 58% of cases have been missed at routine clinical examination.[10] Prevalences and incidences of the disorder at post-mortem examination vary throughout the world (table).[2,12–23] In developed countries, most cases of Wernicke's encephalopathy are in people who misuse

	Prevalence (%)
Australia[2,15,16]	1·7–2·8
Austria[13,17]	0·5–1·3
Belgium[13]	0·1
Czechoslovakia[13]	1·0
France[13,18]	0·4–1·4
Germany[13]	0·3–0·8
Norway[19,20]	0·8
UK[13]	0·5
USA[13,21–23]	0–2·2

Table: **Prevalence of Wernicke's encephalopathy**

alcohol, although there is no obvious correlation between the prevalence of Wernicke's encephalopathy and the per capita consumption of alcohol.[13] Other factors, such as diet, national programmes for supplementation of foods with thiamine, and drinking habits may have a role.[13] In a study on alcohol-related mortality in Italy in 1980–90, the absolute number of alcohol-related deaths for alcoholic psychoses (International Classification of Disease 9 code 291) was 24 (21 males, three females) per 18 033 deaths, 0·1% with respect to all alcohol-related causes of death.[24] However, in this study, the proportion of "alcoholic psychoses" contributed by Wernicke's encephalopathy or Korsakoff's syndrome is undetermined.[24] About 80% of patients with Wernicke's encephalopathy who survive develop Korsakoff's syndrome, a disorder that is principally characterised by severe memory defects, in particular a striking loss of working memory that accompanies relatively little loss of reference memory.[9]

Wernicke's encephalopathy is more common in males than in females (male-to-female ratio 1·7 to 1).[1] The estimated mortality is 17%.[9] The response to thiamine deficiency may be population specific: Asians tend to develop mainly a cardiovascular (wet) beriberi, whereas Europeans tend to develop a dry beriberi with polyneuropathy and Wernicke's encephalopathy.[25] Notably, the incidence of Korsakoff's syndrome in Glasgow has increased substantially in recent years,[14,26] despite the fact that, in this population, the bread has been supplemented with thiamine for many years.[27]

Genetics

In the late 1970s, a biochemical study showed that, in fibroblasts from patients with Wernicke-Korsakoff syndrome (WKS), transketolase had decreased affinity for thiamine pyrophosphate.[25] The abnormality persisted through several generations of culture medium in the presence of excess thiamine and absence of ethanol.[25] Thus, the occurrence of this enzyme variant may put individuals at risk for Wernicke's encephalopathy when on a diet marginal or deficient in thiamine. This finding is consistent with other studies in isolated populations and in monozygotic twins concordant for WKS.[28] Although there were some variants in the nucleotide sequence of the transketolase coding region in fibroblasts derived from patients with WKS, there were no aminoacid sequence variations[29] or RNA splicing variants. Other mechanisms, such as post-translational modifications or different assembly of proteins, have been postulated to explain the difference in biochemical activity of transketolase in WKS. Furthermore, variation in the X-linked transketolase-like 1 (*TKTL1*) gene might also contribute to genetic susceptibility to WKS.[30]

Other findings provide evidence for a role of the GABA$_A$ receptor subunit gene cluster on chromosome 5q33 in susceptibility both to the alcohol-dependence syndrome and Korsakoff's syndrome.[31] More recently, another gene coding for the high-affinity thiamine transporter protein

SLC19A2 has been implicated in the pathophysiology of WKS.[32,33] Mutation screening identified three new genetic variants in the 3′ untranslated region of the high-affinity thiamine transporter in 25 people with alcoholism and WKS.[33] The 3′ untranslated region is important in terms of gene regulation and protein expression.[34] Subtle genetic changes in the effectiveness of the various transport systems of thiamine in patients who develop Wernicke's encephalopathy might ultimately lead to diminished ability to transport thiamine into brain cells.[32] This functional impairment could contribute to an individual's ability to cope with thiamine deficiency or respond to therapy.[35] However, other studies are needed to further define the significance of these findings.

Several variants in genes that encode enzymes involved in alcohol metabolism might be risk factors for WKS. However, in 47 people with alcoholism with WKS, the prevalence of only the aldehyde dehydrogenase-2 ADH2*1 allele was high.[36] Moreover, some gene polymorphisms, although not directly involved in the pathogenesis of WKS, might have a modifying role in the severity of clinical phenotype. One of the best characterised is the APOE ε4 allele, a well-known risk factor for Alzheimer's disease. In patients with WKS and global intellectual deficiency, the frequency of the ε4 allele is significantly higher than in patients with WKS and preserved intellectual function other than amnesia, suggesting the involvement of this allele in the intellectual decline of patients.[37]

In WKS several genetic defects might combine with environmental factors to generate the phenotype, and these genetic defects become clinically important when the diet is deficient in thiamine.

Pathophysiology

Thiamine deficiency leads to brain lesions—usually restricted to selective, vulnerable regions, with high thiamine content and turnover—within 2–3 weeks.[38] This timescale is related to the time necessary to deplete the body's stores of thiamine, which are only sufficient for up to 18 days.[39] After about 3 weeks of thiamine deficiency, the blood levels of thiamine also fall,[40] leading to impaired function of enzymes requiring thiamine pyrophosphate as a coenzyme.[38,39] Thiamine is absorbed in the duodenum by an active, carrier-mediated, rate-limited process,[8] and at the blood–brain barrier, its transport occurs through both passive and active mechanisms.[8,41] In neuronal and glial cells, thiamine is converted to thiamine pyro-phosphate, which is necessary for several biochemical pathways in the brain, such as intermediate carbohydrate metabolism (for energy production by ATP synthesis), lipid metabolism (for production and maintenance of myelin sheath), and production of aminoacids and glucose-derived neurotransmitters (eg, glutamic acid; GABA).[3] Thiamine also seems to have a role in acetyl-cholinergic and serotoninergic synaptic transmission and axonal conduction.[42]
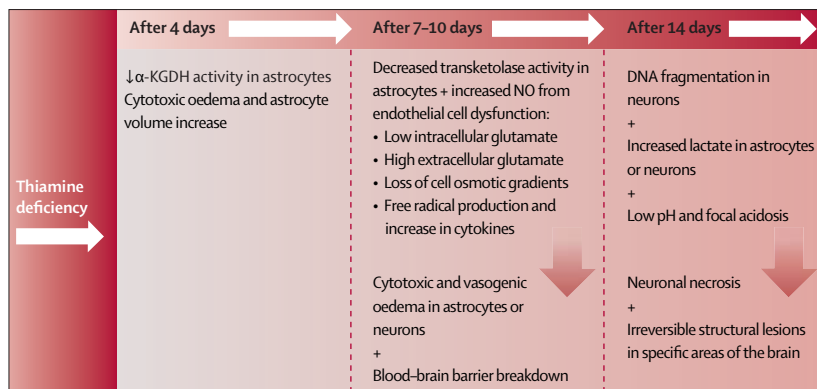
Figure 1: **Proposed temporal sequence of metabolic and morphological changes during thiamine deficiency**
α-KGDH=α-ketoglutarate dehydrogenase complex; NO=nitric oxide.

At the cellular level, the major enzymes involved are the α-ketoglutarate-dehydrogenase complex and the pyruvate-dehydrogenase complex in the tricarboxylic acid cycle, and transketolase in the pentose-phosphate pathway.[43] The earliest biochemical change is the decrease in α-ketoglutarate-dehydrogenase activity in astrocytes, which occurs after about 4 days of thiamine deficiency.[44,45] This is consistent with findings from animals with experimental thiamine deficiency, which consistently show early damage to glial cells rather than neurons,[46,47] and patients with WKS, who have changes in astroglia together with microglial proliferation apparent even in regions of the brain with little if any neuronal cell death.[23]

A reduction in the activity of transketolase is noticed after about 1 week of thiamine deficiency, whereas no change in the activity of pyruvate dehydrogenase is observed for up to 10 days.[44] This metabolic impairment produces a diffuse decrease in the use of glucose in the
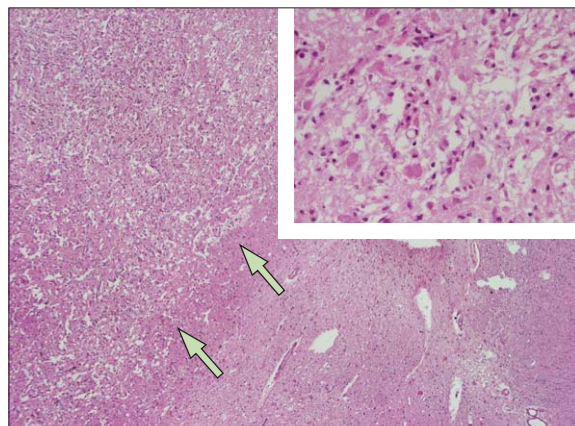

Figure 2: **Low-power view of thalamic tissue in a patient with Wernicke's encephalopathy**
Main image: prominent cytoarchitectural changes are indicated by arrows (H&E, original magnification: 40 X). Inset: characteristic loosening of the neuropil, proliferation of small vessels and the presence of reactive astrocytes, with relative neuronal and axonal sparing, are visible (H&E, original magnification: 200 X).

brain,[48] with consequent severe impairment of cellular energy metabolism.[48] In particular, many astrocyte-related functions are impaired, such as the control of intracellular and extracellular glutamate concentrations (with probable occurrence of glutamate-mediated excitotoxicity), the maintenance of ionic gradients across the cell membrane, and blood–brain barrier permeability.[49]

Moreover, in Wernicke's encephalopathy at the symptomatic stage, increased lactate production by both neurons and astrocytes has been noticed, with intracellular accumulation of lactate, reductions in pH, and focal acidosis.[50] DNA fragmentation in thalamic neurons resulting in apoptotic cell death appears after about 2 weeks of thiamine deficiency.[51] Other mechanisms involved include mitochondrial dysfunction and intracellular oxidative stress with production of free radicals and cytokines as a result of early endothelial-cell dysfunction and increased production of nitric oxide.[52] The main consequence of these metabolic changes is the loss of osmotic gradients across cell membranes, with cytotoxic oedema and a progressive cell-volume increase firstly in astrocytes, then in neurons[53] (figure 1).

Decreased α-ketoglutarate-dehydrogenase activity resulting from thiamine deficiency, changes in the synthesis of aminoacids, and the accumulation of lactate in the brain are initially reversible after prompt and sufficient thiamine therapy—the so-called stage of "reversible biochemical lesion".[49] Conversely, a lack or delay of thiamine rehabilitation may lead to structural, irreversible lesions in selective regions of the brain with possible permanent neurological sequelae or a fatal outcome.[23]

Neuropathology

Macroscopic and microscopic features depend on the stage and the severity of Wernicke's encephalopathy.[54] About 50% of patients have symmetrical, greyish discolouration, congestion, and fresh pinpoint haemorrhages, mainly in the periaqueductal grey matter, the mamillary bodies, and medial thalamus.[9] Typical histopathological changes affect specific areas of the brain,[9] such as the medial dorsal thalamic nucleus bilaterally, in 100% of patients.[9] The superior vermis of the cerebellum is involved in a third of cases.[9] Other areas sometimes affected include the periaqueductal region, the pontine tegmentum, the reticular formation of the midbrain, the posterior corpora quadrigemina, and the cerebral cortex.[9] On histological examination, acute lesions caused by extreme rapidity of thiamine deficiency show a symmetrical distribution of multiple, small, new haemorrhages in the brainstem and the thalamus, with some spongiosis between the haemorrhages without interstitial infiltration of macrophages and without relevant capillary proliferation.[55] Chronic lesions show swelling of astrocytes, minimal

loss of neurons, oedema, a decrease in myelinated fibres, activated microglia, reactive astrogliosis, and prominent vessels as a result of swelling and hyperplasia (figure 2).[9,54]

Clinical spectrum of thiamine deficiency

In an individual, the symptoms or signs of thiamine deficiency may vary greatly according to the clinical setting and patient's age and genetic susceptibility. Neurological or cardiovascular disturbances are present and may coexist in one patient. The involvement of the cardiovascular system may take two forms: a common, high-output state characterised by heart failure, orthopnea, and pulmonary and peripheral oedema, and a rare, low-output state, characterised by severe hypotension, lactic acidosis, and absence of oedema. Severe, short-term thiamine deficiency commonly induces Wernicke's encephalopathy, whereas a mild to moderate, prolonged deficiency preferentially leads to damage to peripheral nerves. This polyneuropathy tends to be worse distally than proximally and involves myelin more than axons. A peculiar form is the infantile beriberi that occurs in infants breastfed by mothers with thiamine deficiency, or in infants fed with soy-based formulae defective in thiamine, usually at age 2–12 months.[56–59] Cardiomyopathy, aphonia, absent deep-tendon reflexes, vomiting, diarrhoea, weight loss, restlessness, nystagmus, ophthalmoplegia, and respiratory symptoms may co-occur.

Clinical features

Early detection of subclinical thiamine deficiency is a difficult task, as symptoms may be vague and non-specific, such as frequent headaches, fatigue, irritability, abdominal discomfort, and decline in the growth rate of children.[39] Definite thiamine deficiency presents with Wernicke's encephalopathy, which has an acute onset and is characterised by mental status changes, ocular abnormalities, and motor problems, such as gait incoordination and ataxia. About 82% of patients have mental status changes according to autopsy-based series.[2] These changes largely result from an involvement of thalamic or mamillary bodies and range from a confusional state to mental sluggishness, apathy, impaired awareness of the immediate situation, inability to concentrate and, if left untreated, coma and death.[1,2,4] Some patients may present with confusion or agitation, hallucinations, and behavioural disturbances, mimicking an acute psychotic disorder.[60,61] Ocular abnormalities, occurring in about 29% of patients, include nystagmus, symmetrical or asymmetrical palsy of both lateral recti or other ocular muscles, and conjugate-gaze palsies, which result from lesions of the pontine tegmentum and of the abducens and oculomotor nuclei.[1] A few patients have sluggish reaction of the pupils to light, anisocoria, and light-near dissociation.[62] Bilateral visual disturbances with optic-disk oedema, sometimes with retinal haemorrhages, may be the presenting features of Wernicke's encephalopathy.[63] Loss of equilibrium with incoordination of gait and trunk ataxia affect about 23% of patients and result from an involvement of cerebellar vermis and vestibular dysfunction.[1,64] The coexistence of polyneuropathy may be a contributing factor. A few patients have limb ataxia and dysarthria.[1]

About 19% of patients have none of the symptoms of the classic triad at the presentation of Wernicke's encephalopathy,[2,19] although usually one or more symptoms appear later in the course of the disease.[10,65] Other presenting symptoms may be stupor (mainly related to damage within the thalami); hypotension and tachycardia caused by either a defect in efferent sympathetic outflow or a coexistent cardiovascular beriberi; hypothermia resulting from involvement of the posterior hypothalamic regions; epileptic seizures caused by excessive glutamatergic activity; and progressive hearing loss, probably secondary to thalamic involvement.[66–68]

Little is known about the temporal progression of neurological signs in Wernicke's encephalopathy. A few days after the first symptoms, other signs may appear: spastic paresis secondary to involvement of motor cortex or pyramidal tracts; hyperthermia, unresponsive to antipyretics, caused by involvement of anterior hypothalamic regions; increased motor tone with nuchal and lower-spine rigidity; and choreic dyskinesias caused by damage to structures at mesopontine tegmental areas.[10,65,67] To facilitate the diagnosis, we classified the clinical features of Wernicke's encephalopathy in symptoms common at presentation, uncommon at presentation, and late-stage symptoms (panel 1).

Caine and co-workers[69] devised operational criteria to significantly improve the identification of patients with alcoholism and Wernicke's encephalopathy. The existing

classic triad was modified to include the presence of dietary deficiencies and required only two, rather than three, signs for a clinical diagnosis. Using this criterion, the diagnosis of the disorder, either alone or with severe and stable amnesia that does not remit with thiamine treatment (Korsakoff's syndrome), can be achieved with a large degree of specificity and sensitivity.[69] Wernicke's encephalopathy was under-recognised only when occurring with hepatic encephalopathy (50% sensitivity).[69] Importantly, because in this study the neuropathological findings indicate that patients with alcoholism with hepatic encephalopathy have a high risk of additional Wernicke's encephalopathy, these patients might benefit from treatment with parenteral thiamine.[69]

Predisposing factors and clinical settings

In recent years, there has been an increase in the number of clinical settings in which Wernicke's encephalopathy

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Panel 2: Clinical settings related to Wernicke's encephalopathy

Staple diet of polished rice

Chronic alcohol abuse and malnutrition

Gastrointestinal surgical procedures
Surgical procedures: gastrectomy; gastrojejunostomy; partial or subtotal colectomy; gastric bypass surgery; vertical banded gastroplasty; therapy with an intragastric balloon
Disorders: peptic ulcer; gastric cancer; colon cancer; ulcerative colitis with megacolon; severe obesity

Recurrent vomiting or chronic diarrhoea
Pyloric stenosis; peptic ulcer; drug-induced gastritis; biliary colics; Crohn's disease; intestinal obstruction or perforation; lithium-induced diarrhoea; migraine attacks; anorexia nervosa; pancreatitis; hyperemesis gravidarum

Cancer and chemotherapeutic treatments
Cancer and related conditions: gastric carcinoma; non-Hodgkin's lymphoma; myelomonocitic leukaemia; large B-cell lymphoma; myeloid leukaemia; allogenic bone marrow transplantation
Chemotherapeutics: erbulozole; ifosfamide

Systemic diseases
Renal diseases; AIDS; chronic infectious febrile diseases; thyrotoxicosis

Magnesium depletion
Secondary to chronic diuretic therapy; intestinal tract resection; Crohn's disease

Use of chemical compounds and drugs
Intravenous infusion of high-dose nitroglycerin; tolazamide

Unbalanced nutrition
Absolute deficiency of food/thiamine: dietary restrictions owing to economic reasons or political trade embargoes; psychogenic food refusal; fasting for religious-philosophical reasons; starvation for treatment of obesity; hunger strike; neglect in old age or Alzheimer's disease
Relative deficiency of thiamine: unbalanced total parenteral nutrition; unbalanced intravenous hyperalimentation; re-feeding syndrome; use of dietary commercial formulae; slimming diets; excessive cooking of food; chronic use of food containing thiaminases or antithiamine factors; chronic use of sulphites as food additives (dogs)

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is observed. Those more commonly encountered in clinical practice are discussed below (panel 2).

Staple diet of polished rice

About two-thirds of the world's population have rice as the main part of the diet. Polished, white rice is highly deficient in thiamine because milling removes the husk, which contains most of the thiamine. In Asian countries, beriberi and not Wernicke's encephalopathy has been endemic as long as the population used preferentially polished rice.[58] As the populations started to use thiamine-enriched food, the incidence of beriberi decreased.

Alcohol misuse and malnutrition

Chronic alcohol misuse does not result in Wernicke's encephalopathy if the dietary intake of thiamine is adequate.[70,71] Contributing factors to thiamine deficiency in those who misuse alcohol are self-neglect, the low content of vitamins and minerals in alcoholic beverages, the decreased transport of thiamine across intestinal mucosa, the low capacity of the liver to store the vitamins, and the impaired conversion of thiamine to the active compound thiamine pyrophosphate.[27] Moreover, the metabolism of alcohol raises the demand for thiamine, so that alcohol-dependent people typically require more of the vitamin than non-alcoholic people do.[72] Because not every individual with a similar degree of malnutrition and alcohol misuse develops Wernicke's encephalopathy, both environmental and genetic factors are likely to contribute to disease expression.[25] In any case, the risk for the disorder in patients with alcoholism is high and, in several countries, this encephalopathy is most commonly associated with chronic alcohol misuse.[8,66] In Australia, the enrichment of bread flour with thiamine has caused a 40% reduction of the incidence of Wernicke's encephalopathy and Korsakoff's syndrome.[73,74] However, other factors may have had a contributing role in the decline of incidence, such as a change in the total per capita alcohol consumption, a change in the pattern of drinking, and an increase in the number of alcoholism-treatment centres.[75] The mandatory enrichment of staple food (ie, grain products) with thiamine is also operative in the USA and the UK, and it is under consideration in Italy and other member of the European Union.[76]

Gastrointestinal surgery

Most of the surgical procedures that lead to exclusion of portions of the gastrointestinal tract are risk factors for the development of Wernicke's encephalopathy, poly-neuropathy, and wet beriberi.[77–79] After surgery, low levels of thiamine and other nutrients (eg, niacin, pyridoxin, vitamin B12, iron) can lead to multivitamin deficiency. The surgical procedures implicated include gastrectomy, gastrojejunostomy, colectomy, gastric bypass surgery, vertical banded gastroplasty, and therapy with an intra-gastric balloon.[77–80] The disorders treated with such procedures include peptic ulcer disease, gastric cancer,

colon cancer, ulcerative colitis with toxic megacolon, and severe obesity with a body-mass index of 40 or higher.[77–80] Wernicke's encephalopathy occurs most commonly 2–8 months after surgery, mainly in individuals with weight loss greater than 7 kg per month.[61,79,81] A few patients develop the disorder as early as 2 weeks postoperatively and as late as 20 years after gastrectomy.[81,82] Early occurrence of Wernicke's encephalopathy after surgery may be fostered by intravenous hyperalimentation without thiamine supplementation,[80] whereas a late occurrence may be associated with a minor change in dietary habit that may precipitate a long-standing latent deficiency of thiamine.[82] The mechanisms responsible for Wernicke's encephalopathy after gastrointestinal surgery include the occurrence of vomiting, poor compliance with an adequate dietary intake, the limited amount of food ingested, poor digestion of food with consequent malabsorption and the reduced area of the gastric and duodenal mucosa useful for absorbing thiamine.[79] Because of the ever increasing number of people with a morbid obesity, in the past few years, the number of surgical procedures has been constantly increasing,[83] as has the number of published cases of Wernicke's encephalopathy-related to these surgical procedures. In a recent systematic review,[84] the authors conclude that Wernicke's encephalopathy after bariatric surgery usually occurs between 4 and 12 weeks postoperatively, especially in young women with vomiting. Atypical neurological features are common.

Recurrent vomiting and chronic diarrhoea

Various gastrointestinal disorders associated with recurrent vomiting and chronic diarrhoea may result in Wernicke's encephalopathy. These include pyloric stenosis and peptic ulcers, drug-induced gastritis, recurrent biliary colics with vomiting, Crohn's disease, primary intestinal malabsorption, and intestinal obstruction or perforation.[85–88] A case of Wernicke's encephalopathy related to malabsorption due to a lithium-induced persistent diarrhoea has been reported.[89] Other settings include the occurrence of vomiting during migraine attacks,[90] self-induced vomiting in anorexia nervosa,[91] and vomiting with possible diarrhoea and malnutrition due to acute or subacute pancreatitis.[92] A peculiar syndrome is the occurrence of persistent and severe nausea and vomiting in pregnancy that can progress to hyperemesis gravidarum.[93] Thiamine deficiency may occur in pregnancy,[94] even with a standard prenatal thiamine supplementation,[94] and, if inadequately treated, hyperemesis gravidarum may lead to Wernicke's encephalopathy, central pontine myelinolysis, and death.[93]

Cancer and chemotherapeutic treatments

Thiamine deficiency related to cancer was first reported in a patient with acute myeloid leukaemia with heart failure that responded to treatment with thiamine.[95] Wet beriberi or Wernicke's encephalopathy occurs occasionally both in patients with early-stage cancer and in terminally ill patients.[96,97] Moreover, malignancy is the most common underlying disorder that heralds Wernicke's encephalopathy onset in children.[10] Several kinds of cancer have been associated with the disorder, including inoperable gastric carcinoma, non-Hodgkin's lymphoma, myelo-monocytic leukaemia, large B-cell lymphoma, myeloid leukaemia, and allogenic bone-marrow transplantation, in which thiamine deficiency was caused by a lack of thiamine supplementation during total parenteral nutrition.[95–98] In these patients, factors that contribute to the occurrence of thiamine deficiency include the consumption of thiamine by fast-growing neoplastic cells, poor dietary intake related to lack of appetite and nausea, significant malabsorption,[90] and the use of specific types of chemotherapy.[97]

Toxicity related to interference with thiamine has been documented for some chemotherapeutic drugs. For erbulozole, a dose-limiting toxicity has been documented at 100 mg/m^2 (one dose every 3 weeks) and 50 mg/m^2 (weekly administration). At these doses, patients can show a dose-limiting Wernicke's encephalopathy-like syndrome.[99] Recently, a syndrome related to ifosfamide that may be reversed by the administration of thiamine has been reported.[100] Because the concentrations of thiamine in blood did not change after erbulozole or ifosfamide were given, it has been suggested that these drugs or their metabolites might interfere with thiamine function or the enzymes of the intermediate carbohydrate metabolism.[99,100] In particular, both drugs may interfere with the activation of thiamine pyrophosphate from thiamine.[99,100]

Systemic diseases

Many systemic diseases that affect thiamine intake and metabolism may predispose susceptible individuals to the development of Wernicke's encephalopathy. Patients receiving both peritoneal dialysis and haemodialysis are susceptible to the disorder.[101] The factors fostering a thiamine deficiency in these patients are the low intake of the vitamin due to anorexia and vomiting, the accelerated loss of thiamine during dialysis, the occurrence of infections, and the use of intravenous or intradialytic parenteral nutrition without thiamine addition.[102] Some patients with uraemic encephalopathy have a high brain concentration of guanidosuccinic acid.[103] This compound may inhibit the enzyme transketolase, thus further predisposing these patients to Wernicke's encephalopathy. Because clinical differentiation of Wernicke's encephalopathy from other neurological complications that may occur in these patients can be difficult,[103] any patient in regular dialysis presenting with encephalopathy and unexplained neurological symptoms should be given parenteral thiamine.

Post-mortem diagnosis of Wernicke's encephalopathy in a patient with AIDS treated with zidovudine was first

reported in 1987.[104] In 1991, Butterworth[11] reported evidence of thiamine deficiency in 9 of 39 (23%) patients with AIDS or AIDS-related complex, without clinical evidence of Wernicke's encephalopathy.[11] Recent reports confirm that encephalopathy may play a part in the morbidity and mortality associated with AIDS.[105] The cachexia and the catabolic state characteristic of AIDS predispose to Wernicke's encephalopathy in these patients.[11] Because of the difficulties of clinical diagnosis, dietary thiamine supplementation is recommended in all newly diagnosed cases of AIDS or AIDS-related complex,[11] especially where access to antiretroviral therapy is limited.[105]

Several authors[1,20,106] mention the possible occurrence of Wernicke's encephalopathy after prolonged infectious febrile diseases (eg, bronchopneumonia of undetermined nature).[20,106] In these patients, thiamine deficiency seems to be due to increased requirement of the vitamin, sometimes associated with deficient oral intake.[20]

Wernicke's encephalopathy may be related either to severe hyperthyroid Grave's disease[107] or to gestational thyrotoxicosis associated with hyperemesis gravidarum.[108] Factors fostering thiamine deficiency seem to be the hypermetabolic state characteristic of thyrotoxicosis and, eventually, the occurrence of malabsorption due to vomiting and diarrhoea.[107]

Magnesium depletion
Magnesium as a cofactor has a crucial role in the proper catalytic action of many enzymes, including transketolase in the pentose phosphate pathway[109] and thiamine pyrophosphokinase in the conversion of thiamine into thiamine pyrophosphate.[109] Moreover, its severe deficiency may lead to a refractory response to thiamine until magnesium is given.[110] Patients on long-term diuretic therapy or with intestinal tract resection or Crohn's disease can develop Wernicke's encephalopathy.[111] Magnesium deficiency may also play a part in fostering the disorder in individuals who chronically misuse alcohol, patients with hyperemesis gravidarum, and patients with hypochlorhydria.[111]

Use of chemical compounds and drugs
A mild thiamine deficiency may be found in individuals after chronic exposure to formaldehyde, or to several prescription drugs such as phenytoin, cephalosporins, and tetracyclines.[39] However, the clinical relevance of this deficiency is uncertain. The intravenous infusion of high-dose nitroglycerin in human beings has been associated with the occurrence of Wernicke's encephalopathy, probably caused by a metabolic effect of the diluent ethyl alcohol and propylene glycol on thiamine metabolism.[112] By contrast, the oral hypoglycaemic agent tolazamide can cause Wernicke's encephalopathy by further lowering thiamine concentrations in susceptible individuals with depleted thiamine concentrations.[113]

Unbalanced nutrition
Because the body's reserves of thiamine are sufficient for up to 18 days,[39] in a healthy individual, any condition of unbalanced nutrition that lasts 2–3 weeks may lead to Wernicke's encephalopathy. In individuals with marginal stores of thiamine, the disorder may occur earlier, particularly if the diet has been very rich in carbohydrates.[114] Absolute thiamine deficiency may result from dietary restrictions due to economic or sociopolitical reasons,[115] a background of psychogenic food refusal (as in patients with anorexia nervosa, depressive illness, or schizoaffective psychoses),[90,116,117] prolonged fasting for religious-philosophical reasons,[118] prolonged starvation for the treatment of obesity,[119] hunger strike in political prisoners,[120] or Alzheimer's disease or neglect in old age.[75,121] Relative deficiency occurs when dietary intake of thiamine is insufficient in relation to physiological state, total caloric intake, and the proportion of calories provided as carbohydrates. Relative deficiency may occur in patients who develop Wernicke's encephalopathy during total parenteral nutrition without proper replacement of thiamine,[122] in patients on intravenous hyperalimentation with a high percentage of glucose not balanced with adequate doses of thiamine,[122] or during the early postoperative oral food intake period after several days of intravenous nutrition without adequate vitamin supplementation (refeeding syndrome).[80] Commercial dietary formulae, with or without thiamine, in infants or ill patients[59,123] and the use of prolonged unbalanced, or apparently balanced slimming diets[124] in obese women, or food faddism can lead to thiamine deficiency. Because these formulae and diets contain thiamine in amounts that conform to standard nutritional recommendations, the occurrence of Wernicke's encephalopathy after their use is not something we would predict on general principles. However, supplements to these diets frequently include herbal preparations. Herbal preparations may interfere with thiamine's duodenal absorption or act as thiamine antagonists.[124–126] A soy-based formula for infants used in Israel in 2003[59] led to a severe deficiency in thiamine (<0·5 µg/g), despite the amount of thiamine reported on the label.[59] Thus, these products do not seem to be well monitored by public-health authorities, and the quality controls may be poor.

Lastly, thiamine in food may be inactivated by excessive cooking, the regular use of antacids, which may interfere with the absorption of thiamine, the consumption of food containing thiaminases (such as certain raw fish and shellfish that contain bacteria rich in thiaminases),[127] or the regular use of high amounts of tea, coffee, decaffeinated coffee, and betel nut, which contain antithiamine factors.[125–127] Critical concentrations of sulphites in food may destroy thiamine, and a Wernicke's encephalopathy-like syndrome has been reported after prolonged feeding of dogs with sulphite-preserved meat.[128]
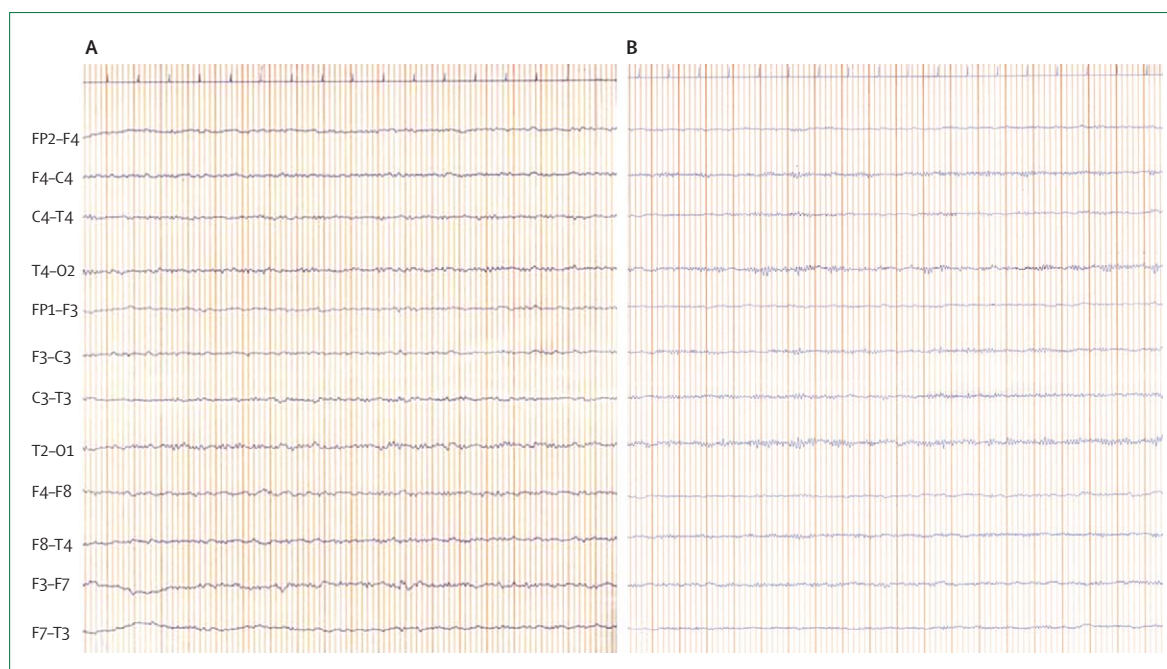
Figure 3: **Electroencephalography in late-stage Wernicke's encephalopathy**
Diffuse slow waves in the theta range of a patient about 2 weeks after onset of neurological symptoms (A). Healthy control tracing (B).

Data indicate that patients who develop Wernicke's encephalopathy in association with alcohol misuse require much larger parenteral doses of thiamine and are more likely to develop Korsakoff's syndrome than those who do not misuse alcohol.[32,129] This may be due to the fact that non-alcoholic patients may present at an earlier stage of the disorder, may have more obvious symptoms, and may engender a more active treatment response.[32] Furthermore, Korsakoff's syndrome in patients with alcoholism might result from the accumulation of lesions during repeated subclinical episodes of thiamine deficiency,[2,130,131] with ethanol neurotoxicity being a possible contributing factor,[132,133] whereas patients without alcoholism usually experience thiamine deficiency only once and for a relatively short period of time.[129]

Korsakoff's syndrome

Korsakoff's syndrome is defined as a disproportionate impairment in memory, relative to other features of cognitive function, resulting from nutritional (thiamine) deficiency.[134] In particular, the syndrome is characterised by a chronic striking loss of working memory with relatively little loss of reference memory.[135–137] Korsakoff's syndrome usually follows or accompanies Wernicke's encephalopathy, with the typical clinical pattern emerging when the acute global confusional state of the latter resolves. Prompt treatment of Wernicke's encephalopathy with adequate doses of parenteral thiamine may prevent the development of Korsakoff's syndrome, but this syndrome responds little if at all to thiamine therapy.[138]

Patients with Korsakoff's syndrome present with a severe anterograde amnesia and are unable to remember events even within the previous half an hour, although they retain implicit learning, so these patients can learn new motor skills or develop conditioned reactions to stimuli.[139] Also, memory of events in the weeks or months before the disorder is severely disturbed.[134] Disorientation to time is noticeable. Other cognitive functions are preserved in most patients, or may show only minor deficits (eg, executive functions).[140] Confabulation accompanies the memory defect in the early stages but becomes less apparent after months or years.[134] In addition, emotional changes may develop, including apathy, blandness, or mild euphoria, with little or no reaction to events.[134] The diagnosis is supported by neuroimaging or autopsy findings that show thalamic and mammillary-body degeneration and frontal-lobe atrophy.[141,142] Structural or neurochemical abnormalities within a circuit involving the mammillary bodies, the mammillothalamic tract, and the anterior thalamus may account for anterograde amnesia, whereas frontal-lobe dysfunction may underlie the retrograde amnesia and emotional changes observed.[134,140]

Diagnosis

The high rate of incorrect diagnosis for Wernicke's encephalopathy might be caused by either a relatively non-specific clinical presentation of the disease in some cases or poorly recognised clinical presentation and neurological signs. In particular, the possibility of an incorrect diagnosis is high in alcohol-dependent patients presenting to accident and emergency departments.[8]
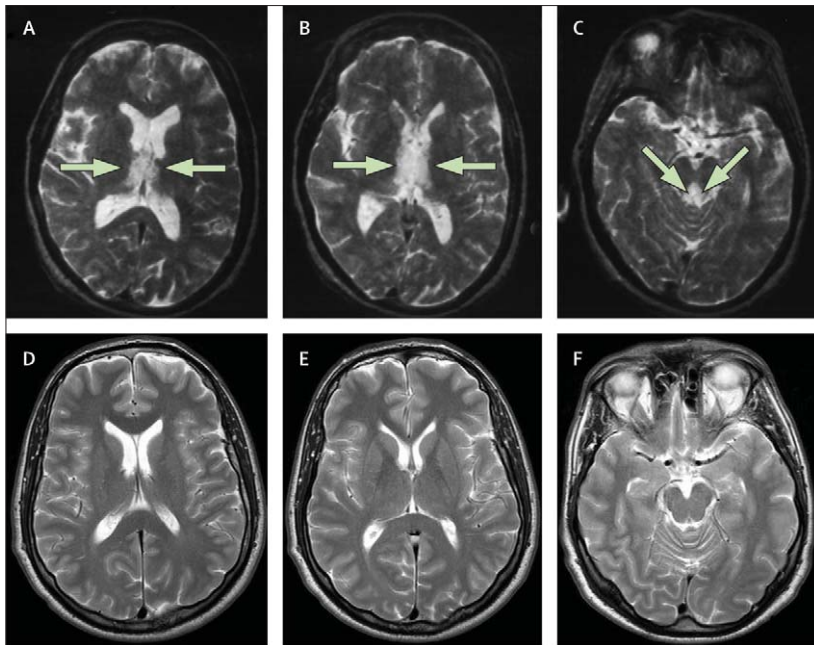
Figure 4: **T2-weighted axial MRI in Wernicke's encephalopathy**
Symmetrical high-intensity lesions in the medial thalami (A, B), as well as in the periacqueductal grey matter of the midbrain (C), are evident in a patient about 2 weeks after onset of neurological symptoms. MRI of a healthy person (D, E, F).

The common signs of Wernicke's encephalopathy are difficult, if not impossible, to differentiate from drunkenness, and such problems need to be highlighted to emergency medicine doctors and nurses as part of their training.[8] The lack of an adequate preparation may result in underdiagnosis and treatment.[32,75,143]

Because there is no specific routine laboratory test available, and no specific diagnostic abnormalities have been revealed in cerebrospinal fluid, brain imaging, electroencephalogram, or evoked potentials, Wernicke's encephalopathy remains a clinical diagnosis. In this regard, the best aid for a correct diagnosis is clinical suspicion, and clinicians should consider the disorder in any patients with unbalanced nutrition or in the clinical setting of subacute or chronic diseases that increase metabolism or alter the ingestion and absorption of food, as well as when patients show only one component of the classic triad. The presumptive diagnosis of Wernicke's encephalopathy can be confirmed by determining blood thiamine concentrations or by measuring the red blood cell transketolase activity.[144,145] However, these measurements are limited by a lack of specificity and technical difficulty.[23] Recently, an isocratic high-performance liquid chromatography method for the assessment of thiamine, thiamine monophosphate, and thiamine diphosphate in human erythrocytes has been described.[146] This procedure has improved reproducibility, practicability, and performance compared with previous methods, and is suitable for both clinical and research purposes.[146]

Other common paraclinical studies include lumbar puncture, electroencephalography, and neuroimaging studies. Cerebrospinal fluid is normal in most patients, although raised protein concentrations can occur in late stages. Results of electroencephalography are within normal limits at an early stage, but show non-specific slowing of the dominant rhythm in a late stage (figure 3). Among paraclinical studies, MRI is currently considered the most valuable method to confirm a diagnosis of Wernicke's encephalopathy. MRI has a sensitivity of only 53%, but its high specificity of 93% means that it can be used to rule out the disorder.[147,148] MRI studies typically show an increased T2 signal, bilaterally symmetrical, in the paraventricular regions of the thalamus, the hypothalamus, mamillary bodies, the periaqueductal region, the floor of the fourth ventricle and midline cerebellum (figure 4).[147,149] Disruption of the blood–brain barrier has been seen in these regions in 6 of the 12 patients studied with contrast-enhanced CT or MRI.[149] Importantly, the typical pattern of lesions on MRI is observed in only 58% of patients.[150] Unusual sites of lesions include cortical regions and the splenium of the corpus callosum.

Valuable adjuncts for an early diagnosis of Wernicke's encephalopathy are diffusion-weighted MRI and proton MR spectroscopy,[151] which may also provide information on the pathophysiology of this encephalopathy. Ultimately, the diagnosis in a living patient is mainly supported by the response of neurological signs to parenteral thiamine.

Differential diagnosis

The MRI signal characteristics and lesion sites are not entirely specific for Wernicke's encephalopathy. Therefore, other possible causes of acute encephalopathies need to be differentiated, particularly when the clinical history does not reveal a definite predisposing factor related to Wernicke's encephalopathy, or when the response of neurological signs to the administration of thiamine is unclear. These conditions include paramedian thalamic infarction (top-of-the-basilar syndrome), ventriculoencephalitis, Miller-Fisher syndrome, primary cerebral lymphoma, Behçet's disease, multiple sclerosis, Leigh's disease, variant Creutzfeldt-Jakob disease, paraneoplastic encephalitis, severe hypophosphataemia, acute intoxication from methyl bromide, and chronic intoxication from bromvalerylurea.[150,152–154]

Management

Wernicke's encephalopathy is a medical emergency, and in patients in whom the disorder is suspected thiamine should be initiated immediately, either intravenously or intramuscularly, to ensure adequate absorption.[75] Because thiamine hydrochloride can be inactivated by heat, its solutions should be fresh. A recent Cochrane review indicates that there is insufficient evidence from randomised controlled trials

to guide the clinician as to the optimum dose, frequency, route, or duration of thiamine treatment for prophylaxis or treatment of Wernicke's encephalopathy due to alcohol misuse.[155] However, studies by Cook, Thompson, and colleagues[8,14,27,32,75,156,157] support several different regimens for patients with the disorder and those at risk of developing it. Specifically, patients who have signs indicative of Wernicke's encephalopathy should be treated empirically with a minimum of 500 mg thiamine hydrochloride (dissolved in 100 ml of normal saline), given by infusion over a period of 30 min, three times per day for 2–3 days. Where there is no response, supplementation may be discontinued after 2–3 days. Where an effective response is observed, 250 mg thiamine given intravenously or intramuscularly daily for 3–5 days, or until clinical improvement ceases, should be continued. Doses of thiamine between 100 mg and 250 mg per day apparently may not restore vitamin status,[158] improve clinical signs,[159] or prevent death.[156] In particular, when patients with Wernicke's encephalopathy are inappropriately treated with low doses of thiamine, the biochemical abnormalities caused by thiamine deficiency can lead to irreversible brain damage.[8,14] This damage may lead to death, with an estimated mortality rate of about 20%, or to the chronic irreversible form of the encephalopathy (Korsakoff's syndrome) in 85% of survivors.[8,14] Recent data from a controlled study into the therapeutic benefits of thiamine in alcohol-dependent patients without clinically apparent Wernicke's encephalopathy indicate that at least 200 mg of parenteral thiamine may be required to improve neurological symptoms.[160] Prophylactic treatment—intramuscular administration of 250 mg thiamine once daily for 3–5 consecutive days—should be used in all people with severe alcohol withdrawal, poorly nourished patients, and people with poor diet and signs of malnutrition.[8,14,156,161]

At present, the only parenteral high-potency B-complex vitamin therapy available in the UK is Pabrinex, which contains thiamine 250 mg in combination with riboflavin, pyridoxine, nicotinamide, and vitamin C.[75] In Italy, thiamine in parenteral preparations is currently available at 2–100 mg per ampoule.[143] According to the above indications for the treatment of Wernicke's encephalopathy, an Italian patient should receive, as a minimum, the improbable number of 15 ampoules per day (ie, the number of ampoules per day to reach the thiamine dose of 500 mg, three times per day).[143] It is highly predictable, as stated by Agabio,[143] that the lack of both an adequate preparation and clear guidelines on dosage and duration of thiamine treatment will continue to result in the prescription of thiamine doses that do not concur with those deemed to be effective in Wernicke's encephalopathy and in the prevention of Korsakoff's syndrome.

It is mandatory that thiamine is given before or concomitantly with intravenous administration of glucose when a diagnosis of Wernicke's encephalopathy is suspected, because glucose alone can precipitate the disorder in thiamine-deficient individuals. This is an absolute necessity for patients who have been drinking alcohol and now present with hypoglycaemia.[8] Moreover, to prevent the development of Korsakoff's syndrome and to treat symptoms of Wernicke's encephalopathy, in all patients with any evidence of chronic alcohol misuse and a poor diet, parenteral thiamine treatment should be initiated immediately while the patients are still drunk and continued for an adequate time for any patient with evidence of Wernicke's encephalopathy when sober.[75] Victor and co-workers[1] found that recovery from the ophthalmoplegia was complete after a few hours, except for a residual, fine, horizontal nystagmus in 60% of patients. Recovery from ataxia occurred after a few days, although in some cases was incomplete. The changes in mental status tended to improve after 2–3 weeks of therapy. Deficiency in other vitamins and electrolytes, especially niacin and magnesium, should also be corrected. Because a higher enteral intake of thiamine is not toxic,[157] thiamine supplementation by mouth should be continued for several months at a dose of 30 mg twice daily.

As Wernicke's encephalopathy has a variable clinical presentation, it is good medical practice to treat with parenteral thiamine (after determining thiamine status) all patients presenting with coma or a stuporous state, hypothermia or hyperthermia of unknown nature, or tachycardia and intractable hypotension of unknown cause, regardless of the symptoms, particularly if there is a known causal factor associated with Wernicke's encephalopathy. In these cases any therapeutic delay may result in permanent neurological damage or death. Conversely, prompt therapy with thiamine may be a life-saving measure.

Parenteral thiamine and unwanted side-effects
Parenteral thiamine administration is generally safe. In a prospective assessment of the safety of thiamine hydrochloride, given as a 100 mg intravenous bolus in 989 consecutive patients (1070 doses), Wrenn and colleagues[162] found one patient with generalised pruritus (major reaction, 0·093%) and 11 with transient local irritation (minor reactions, 1·02%).[163] Moreover, in a retrospective study Wrenn and Slovis[163] found no significant allergic reactions in more than 300 000 patients treated with parenteral thiamine. However, anaphylactic reactions (ie, a true allergic reaction to thiamine) or anaphylactoid reactions (ie, a dose-dependent reaction) may occur occasionally when thiamine is given parenterally.[8] In particular, serious allergic adverse reactions may occur during or shortly after parenteral administration, mainly with intravenous administration. These include anaphylactic shock (rarely fatal), dyspnoea and bronchospasm and cutaneous rash or flushing.[8,14] Because the unwanted side-effects to

Search strategy and selection criteria

This review is based on material known to the authors or identified through searches of PubMed (up to March 2007) for original articles or previous reviews of the subject, using a combination of the following terms: "Wernicke's encephalopathy", "thiamine deficiency", "diagnosis", "pathophysiology", "genetics", and "treatment". Selection of material for inclusion was based on originality, quality, and relevance to the topic.

B vitamins are most commonly seen after multiple administrations when given intravenously, rather than a slow infusion,[164–166] thiamine should be given intravenously diluted with 100 mL of normal saline or 5% glucose, and infused over 30 min.[8,14] Facilities for treating anaphylaxis should be available when thiamine is given, including facilities for cardiopulmonary resuscitation and immediately available intravenous (1:10 000) or intramuscular (1:1000) adrenaline.[8,14]

Conclusions

Any condition of unbalanced nutrition that lasts for 2–3 weeks can lead to thiamine depletion and Wernicke's encephalopathy with damage in selective diencephalic and brainstem areas. Post-mortem findings indicate that prevalence is higher than appreciated. The disorder may occur in people with chronic alcoholism and in a myriad of clinical settings that include gastrointestinal surgery procedures, gastrointestinal disorders associated with recurrent vomiting or chronic diarrhoea, cancer, and chemotherapeutic treatments, systemic diseases such as AIDS, renal diseases, thyrotoxicosis, and magnesium depletion. Some patients may be genetically predisposed to the pathology.

Wernicke's encephalopathy can be difficult to diagnose because of either a relatively non-specific clinical presentation of the disease in some cases, or because of unrecognised clinical data and neurological signs. The diagnosis is clinical and is mainly supported by the dramatic response of neurological signs to parenteral thiamine. Among paraclinical studies MRI is currently considered the most valuable for diagnosis. In patients suspected of having Wernicke's encephalopathy, thiamine should be initiated immediately, with prescription of the parenteral thiamine doses deemed to be effective in Wernicke's encephalopathy and in prevention of Korsakoff's syndrome.

Additional studies are required to define the mechanisms of neuronal cell death in Wernicke's encephalopathy and to explain the predilection of selective brain structures due to thiamine deficiency. Also, randomised controlled trials are needed to define the optimum dose and duration of thiamine treatment for prophylaxis or treatment of Wernicke's encephalopathy and Korsakoff's syndrome in people with chronic alcoholism and in people without alcoholism. Future challenges lie in the identification of patients who may be genetically predisposed to Wernicke's encephalopathy, so that prophylaxis may be set up, and in the development of effective therapies for Korsakoff's syndrome.

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