

# Wernicke's Encephalopathy

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## ABSTRACT

Wernicke's encephalopathy (WE) is caused by thiamine (vitamin B) deficiency and most commonly found in individuals with chronic alcoholism and malnutrition. Clinically, its characteristic features are mental status disorders and oculomotor abnormalities as well as stance and gait ataxia. The diagnosis of WE is frequently missed and delay in treatment can lead to death or Korsakoff's

amnesic syndrome. Thus, in suspected cases of WE, recommendation is not to await confirmation of diagnosis, but to immediately administer high-dose intravenous thiamine and simultaneously treat magnesium deficiency, especially in alcoholics. It is mainly a clinical diagnosis, and can be supported by laboratory tests and imaging studies.

**Keywords:** Wernicke's encephalopathy; Thiamine; Korsakoff's amnesic syndrome

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## INTRODUCTION

Wernicke's encephalopathy (WE) is an acute neuropsychiatric syndrome that results from thiamine (vitamin B1) deficiency and is characterized by a triad of mental-status changes, oculomotor dysfunction and ataxia [1]. Carl Wernicke was the first to describe the clinical and neuropathological characteristics of the encephalopathy. 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 [2, 3]. Korsakoff (1853-1900) described a similar illness in a larger group of patients with acute confusion and peripheral neuropathy. Those who survived had protracted memory disturbance with great difficulty in memorizing recent events. He named the disease "polyneuritic psychosis". In the first decades of the 20th century, it became widely accepted that the acute disease named Wernicke's encephalopathy is caused by a deficiency of thiamine and that Korsakoff's amnesic syndrome or Korsakoff's psychosis (KS) is its chronic sequel. When symptoms of Korsakoff's amnesic syndrome develop, the entire disease process is called Wernicke-Korsakoff syndrome [4]. WE that is not associated with alcohol misuse can usually be treated with smaller oral doses of thiamine. These patients rarely develop KS, indicating that the combined effect of thiamine deficiency and alcohol misuse produces a synergistic effect which is much more detrimental than either alone.

## EPIDEMIOLOGY [5-10]

The incidence of Wernicke's encephalopathy is believed to be higher in the developing nations than developed countries because of the higher incidence of malnutrition and less vitamin supplementation in poorer regions. The male-to-female ratio for Wernicke's encephalopathy is 1.7:1, likely due to alcoholism being 3-4 times more frequent in men than in women. Average age at onset is 50 years. However, Wernicke's encephalopathy can occur in unusual situations, such as in total parenteral nutrition dependent patients during a multivitamin shortage, in persons with hyperemesis gravidarum, or in infants who are fed thiamine-deficient infant formula. Wernicke's encephalopathy typically occurs in adults with risk factors like alcoholism, post bariatric surgery and malnutrition. Race does not predispose to Wernicke's encephalopathy. Wernicke's lesions were observed in 0.8 to 2.8% of the general population autopsies, and 12.5% of alcoholics. This figure increases to 35% of alcoholics if we include patients with cerebellar damage due to lack of thiamine. In a series of autopsy studies held in Recife, Brazil only 7 out of 36 had alcoholic habits, and only a small minority had malnutrition. In a review of 53 published case reports from 2001 to 2011, the relationship with alcohol was also about 20% (10 out of 53 cases). The main factors triggering death are thought to be infections and liver dysfunction.

## ETIOLOGY

WE is caused by the disruption of the thiamine diphosphate (ThDP)-dependent enzymatic activity in susceptible brain cells, commonly secondary to thiamine (Th) deficiency. This correlates directly with three pathogenic entities: WE, cardiovascular beriberi, and neuropathic beriberi. Recently, two other conditions that seem to be directly related to Th deficiency have been described: African (Nigerian) seasonal ataxia and gastrointestinal beriberi [11-13]. Th deficiency also seems to be involved in other diseases like Strachan syndrome (i.e. polyneuropathy, optic neuropathy, orogenital ulcerations), 'tobacco-alcohol amblyopia', tropical ataxic neuropathy (i.e. sensory neuropathy, optic neuropathy, sensorineural deafness), Marchiafava-Bignami disease, subacute 'alcoholic' cerebellar degeneration and epidemic spastic paraparesis (konzo). Th competitive antagonists and/or impaired Th to ThDP conversion may lead to WE even in the presence of normal Th blood levels. Impaired apoenzyme activation due to magnesium (Mg) deficiency and/or decreased activity of the ThDP dependent enzymes may condition the degree of susceptibility to borderline low levels of ThDP. The nervous system and the cardiac muscles are most vulnerable as compared to other systems. The pattern of cellular susceptibility may be influenced by genetic and environmental factors, including the nutritional and hormonal status, and seems not to be homogeneously represented among individuals, thus possibly explaining the preferential expression of one (or more) of the potential pathologic entities related to Th deficiency [14].

### **PATHOPHYSIOLOGY**

Thiamine deficiency and errors of thiamine metabolism are believed to be the primary cause of Wernicke's encephalopathy. Thiamine, also called B1, helps to breakdown glucose. Specifically, it acts as an essential coenzyme to the tricarboxylic acid (TCA) cycle and the pentose phosphate shunt. Thiamine is first metabolized to its more active form, thiamine diphosphate (TDP), before it is used. The body has 2-3 weeks of thiamine reserves only, which are readily exhausted without intake, or if depletion occurs rapidly, such as in chronic inflammatory states or in diabetes. Thiamine is involved in [15-17]:

1. metabolism of carbohydrates, generating energy
2. production of neurotransmitters including

3. glutamic acid and GABA metabolism, necessary for myelin production
4. amino acid modification
5. neuromodulation

Thiamine deficiency in WE causes neurological dysfunction by oxidative damage, mitochondrial injury leading to apoptosis, and directly stimulating a pro-apoptotic pathway [18]. Thiamine deficiency affects both neurons and astrocytes. Thiamine deficiency alters the glutamate uptake of astrocytes, through changes in the expression of astrocytic glutamate transporters EAAT1 and EAAT2, leading to excitotoxicity. Other changes include those due to the GABA transporter subtype GAT-3, GFAP, glutamine synthetase, and the aquaporin 4 channel [19]. Focal lactic acidosis also causes secondary edema, oxidative stress, inflammation and white matter damage [20]. Thiamine deficiency leads to gross pathologic lesions within the brain, especially the periaqueductal grey matter, mamillary bodies, and medial thalamus, all of which have a high thiamine content and metabolism. Neuronal cells convert thiamine to thiamine pyrophosphate, the metabolically active form, which is essential for ATP synthesis, myelin sheath production, and synthesis of neurotransmitters. Within 4 days of developing deficient thiamine levels, there is marked decrease in activity of alpha-ketoglutarate-dehydrogenase within astrocytes. By 7 days, there is reduction in the activity of transketolase and subsequent increase in nitric oxide from endothelial cell dysfunction. This leads to astrocytic and neuronal edema and disruption of the blood-brain barrier. Within 2 weeks of thiamine deficiency, there is evidence of neuronal DNA fragmentation and necrosis, which leads to irreversible lesions within the brain [21-33].

### **RISK FACTORS [34, 35]**

Wernicke's encephalopathy mainly occurs in alcoholics, but it can also occur in the chronically undernourished, and post bariatric surgery. Other causes of Wernicke's encephalopathy include pancreatitis, liver dysfunction, chronic diarrhea, Celiac disease, Crohn's disease, uremia, thyrotoxicosis, hyperemesis gravidarum, malabsorption, gastrointestinal surgery, incomplete parenteral nutrition, starvation/fasting, chemotherapy, renal dialysis, diuretic therapy, stem cell/bone marrow transplantation cancer, AIDS, Creutzfeldt-Jakob

disease and febrile infections.

### CLINICAL FEATURES [36-40]

The clinical features of WE depends on whether the presentation is acute or subacute. Its cardinal features are: 1) disorder of mental status or confusion, 2) oculomotor abnormalities, and 3) stance and gait ataxia. On examination, usually only one or two of these cardinal features are found and all three are evident only in one-third of the patients.

Disorder of mental status: The most common disorder is a global confusional state with lethargy and apathy, often without prominent agitation. Attention, concentration and memory are disturbed, and in more severe cases, delirium tremens, stupor or coma are present.

Oculomotor abnormality: Horizontal gaze-evoked nystagmus is most common and many have vertical nystagmus as well. Also, paresis or palsy of the ocular lateral rectus muscles (abducens nerves) and conjugate gaze paresis (dysconjugate gaze) are frequently present. Other less common ocular signs include anisocoria, diminished pupillary reaction to light, retinal hemorrhages, ptosis, scotomata and papilledema. In severe illness, complete ocular palsy, absent vestibulo-ocular response (absent doll's sign or absent response to ice-water caloric testing of vestibulo-ocular function) or hypothermia and hypotension can be present.

Stance and gait ataxia: Stance and gait ataxia of variable degree is seen in the majority of patients. Its severity varies from mild imbalance and unsteadiness with difficulty in tandem (heel-to-toe) walking to wide-based shuffling or ataxic gait. In the most severe cases, the patient is unable to sit up in bed, to stand or walk, even with considerable assistance.

Polyneuropathy is seen among 60-82% of patients with WE, either affecting only the legs (57%) or both arms and legs (25%). Acute or subacute polyneuropathy can be seen early in or shortly before the presentation of WE. The neuropathy is characterized by reduced or absent heel tendon reflexes, reduced sensation or pain in the distal feet and sometimes muscle weakness. Sensory disturbances start in the feet and can progress proximally, affecting fingers and hands and ultimately involving the proximal arms and legs. Autonomic neuropathy is less common in WE. It can appear in the sympathetic system with

orthostatic hypotension or the parasympathetic system with urinary retention. Vagus nerve can cause dysphagia, hoarseness or weakness of the voice.

Other less common signs: Hypothermia is rare (1-4%), believed to be due to a lesion in the posterior part of the hypothalamus. Hypotension is seen among 2% of patients. Bilateral facial paresis, bulbar paresis or extremity paresis with increased tendon reflexes and positive Babinski are also rare.

### PROGNOSIS [41-45]

Wernicke's encephalopathy is a significantly disabling and potentially lethal condition that can be prevented or reversed if treated early. Administration of thiamine improves the patient's condition to some degree in many cases; however, persistent neurologic dysfunction is common even after treatment. Wernicke's encephalopathy ophthalmoplegia usually resolves briskly with thiamine repletion if administered early in the disease course, and global confusion can improve within hours or days.

Patients with Wernicke's encephalopathy have significant morbidity and mortality related to their thiamine deficiency, particularly if there are no early signs of neurologic improvement after thiamine repletion. Among patients surviving Wernicke's encephalopathy, a percentage develop Korsakoff psychosis. Patients with Korsakoff psychosis often have permanent neurological disability and require long-term institutionalization. Only about 20% eventually recover completely during long-term follow-up. A worse outcome may be expected in late-stage Wernicke's encephalopathy, which is associated with elevated spinal fluid protein levels and diffuse slowing of postsynaptic potentials on electroencephalography.

Studies suggest that up to 80% of patients with Wernicke's encephalopathy may not be diagnosed, which makes estimates of morbidity and mortality rates unreliable.

### DIAGNOSIS [46-49]

Diagnosis of a presumed WE among alcoholics requires evidence of chronic alcohol misuse and any one of the following unexplained features:

- acute confusion (not due to intoxication) or delirium tremens
- decreased conscious level
- memory disturbance

- ophthalmoplegia, nystagmus
- ataxia (not due to intoxication)
- hypothermia with hypotension

Laboratory work up includes:

- Complete blood count (CBC) - to rule out severe anemias and leukemias as causes of altered mental status
- Serum glucose levels - to exclude hypoglycemia and hyperglycemia
- Pulse oximetry and/or arterial blood gas (ABG) measurement - to exclude hypoxia and hypercarbia
- Toxic drug screening – to exclude drug-induced causes of altered mental status
- Lumbar puncture (LP) - to exclude CNS infections

Erythrocyte transketolase levels reliably detect thiamine deficiency but are not necessary for the diagnosis of Wernicke's encephalopathy. In the erythrocyte transketolase activity assay, the extent of thiamine deficiency is expressed in percentage stimulation compared with baseline levels (the thiamine pyrophosphate effect). Normal values range from 0-15%; a value of 15-25% indicates thiamine deficiency, and a value of greater than 25% indicates severe deficiency. Blood pyruvate and lactate measurements are not specific for thiamine deficiency illnesses but are sensitive and helpful, as thiamine is a cofactor of the pyruvate dehydrogenase enzyme, an important enzyme in aerobic metabolism.

Consider an electroencephalogram (EEG) if nonconvulsive status epilepticus is suspected as a potential cause of coma and altered mental status. A head CT scan is an essential initial test for emergency diagnosis of focal neurologic disease, such as intracerebral hemorrhage. In patients who are comatose, CT scan can detect not only intracranial lesions, but also fractures of the skull and minute amounts of blood.

MRI offers a technique to make a definitive diagnosis antemortem, but the sensitivity is poor. Morphometric studies of MRI imaging confirm that patients with Wernicke-Korsakoff syndrome show excessive mamillary body and cerebellar shrinkage, indicating that these are highly specific MRI findings for this kind of encephalopathy.

### TREATMENT [50-52]

Most symptoms will improve quickly if deficiencies are treated early. Memory disorder may be permanent. In patients suspected of WE, thiamine should be started immediately. Blood should be immediately taken to test for thiamine,

other vitamins and minerals levels. Following this, an immediate intravenous or intramuscular dose of thiamine 10 to 20 mg IM is given three times daily for up to 2 weeks. Thiamine administration is usually continued until clinical improvement ceases.

Alcohol abusers may have poor dietary intakes of several vitamins and impaired thiamine absorption, metabolism, and storage so they may require higher doses. Other supplements like cobalamin, ascorbic acid, folic acid, nicotinamide, zinc

and phosphorus (dicalcium phosphate) may be needed. In patients with Wernicke-Korsakoff syndrome, even higher doses of parenteral thiamine 100 mg IV as an initial dose followed by 50 to 100 mg/day IM or IV are recommended.

Additionally, sulbutiamine (synthetic derivative of thiamine) has been useful in controlling exacerbation of fatigue [53]. Gabapentin, with its relation to the inhibitory neurotransmitter GABA, has been tried prophylactically three times a day in low doses to reduce the effects and number of disordered responses to adverse external stimuli [54].

Thiamine hydrochloride 500 mg is given three times daily intravenously for three consecutive days. If the response is positive, the dose should then be lowered to 500 mg daily and is given intravenously or intramuscularly for five more days. If there is no response after the first three days, the treatment should be stopped, and an alternative diagnosis should be sought. The other modality of treatment includes thiamine hydrochloride 200 mg given three times daily intravenously until there is no further improvement in the signs and symptoms. Thiamine hydrochloride can be administered slowly intravenously [55-57]. Anaphylactoid reactions may occur very occasionally following administration of parenteral thiamine. A history of asthma, atopy and other allergies should be obtained, a record card is given to the patient and a central record is kept of the administration. Adverse reactions are less common with the IM preparation and are more likely to occur after multiple administrations or when given IV as a bolus [58].

### CONCLUSION

WE is a potentially fatal but easily treatable disease common in thiamine deficient alcoholics and/or malnourished susceptible individuals. The classical clinical hallmark consists of oculomotor signs, stance and/or gait ataxia and mental status

changes having acute or subacute onset. No laboratory investigation can accurately exclude the diagnosis of WE, however, the imaging and laboratory workup is useful for supporting the diagnosis and excluding comorbidities. Specifically, oral thiamine is not absorbed to an extent sufficient to replace thiamine stores in WE and should not be used. The administration of high dose parenteral thiamine should be initiated as soon as possible in all patients with suspected WE.

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