Wernicke's encephalopathy in chronic alcoholics

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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 key features are mental status disorders and oculomotor abnormalities as well as stance and gait ataxia. The diagnosis of WE is frequently missed although delay of appropriate treatment can lead to death or Korsakoff´s amnestic syndrome. It is therefore crucial in suspected cases of WE, not to await confirmation of diagnosis, but immediately administer high-dose intravenous thiamine and simultaneously treat magnesium deficiency. Alcoholics at risk of WE should immediately on admission receive prophylactic therapy with parenteral thiamine

Introduction

Wernicke's encephalopathy (WE) is caused by thiamine (vitamin B1) deficiency, deriving from malnutrition of various sources and most commonly found in patients with chronic alcoholism. WE is a clinically underdiagnosed, acute or subacute illness that can cause permanent memory disturbance or death if proper treatment is not given in time. Thiamine deficiency can also cause cerebellar degeneration (alcoholic cerebellar degeneration, nutritional cerebellar degeneration) and neuropathy (alcohol neuropathy, thiamine deficiency neuropathy). [1]

WE was first described in 1881 by the German physician Carl Wernicke (1848-1905) as an acute illness affecting two men with chronic alcoholism and a young woman with protracted vomiting after drinking sulfuric acid in a suicide attempt. Their symptoms and signs were acute confusion, impairment of consciousness, paresis of ocular muscles, nystagmus and unsteady or ataxic gait. All three died after a short course of illness. Neuropathology revealed punctate hemorrhages around the third and fourth ventricles and aqueduct. Wernicke named the disease "acute superior hemorrhagic polioencephalitis".[2,3] During 1887 through 1889, a Russian physician Sergei S. 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"[4.] 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 amnestic syndrome or Korsakoff´s psychosis (KS) is its chronic sequel Should symptoms of Korsakoff´s amnestic syndrome develop, the entire disease process is called Wernicke-Korsakoff syndrome.[1]

Epidemiology

Information on the prevalence and epidemiology of WE derives for the most part from neuropathologic studies. Lifetime prevalence of WE in the developed world is probably around 1.0% (0.4-2.8% according to various studies).[1, 5-9] Most patients have a clear history of malnutrition and 77-90% have chronic alcoholism.[6, 10] In neuropathologic studies, WE is found in 8.9-12.5% of individuals with chronic alcoholism[5, 11.] It is also seen in non-alcoholic patients with malnutrition of various causes, such as protracted starvation[12] or hyperemesis gravidarium[13, 14.] WE can be a consequence of gastrointestinal operations for morbid obesity or other operations on the gastrointestinal tract.[15] It can also result from infusion of glucose solutions[16] or parenteral nutrition[17] without proper thiamine supplementation. It has been diagnosed among patients on hemo- and peritoneal dialysis[18, 19] in patients with various cancers, after bone marrow transplantation [20-22] and in patients with AIDS.[23, 24]
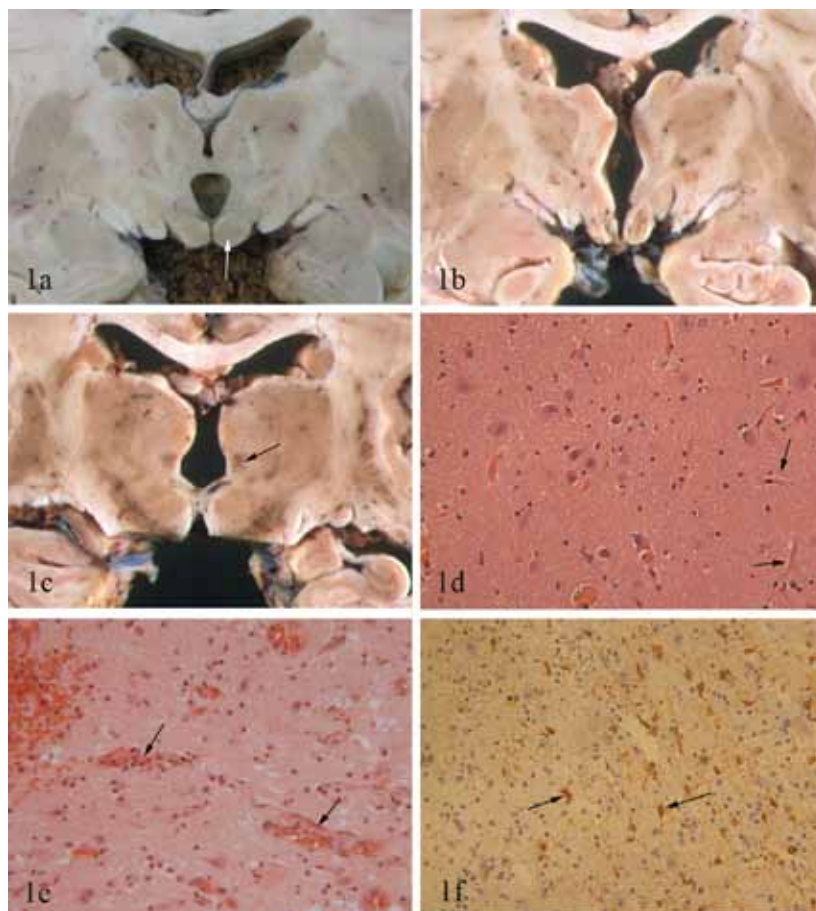
Pathophysiology

Thiamine is a water soluble vitamin, absorbed in the small intestine, and is found in various food products. The daily requirements for adults is approximately 1 mg and total body stores

Figure 1: *Normal mamillary bodies (arrow) (fig. 1a). Mamillary bodies in Wernicke's encephalopathy. Microhemorrhages (dark spots) and soft and granular parenchyma (fig. 1b). Symmetrical microhemorrhages in the hypothalamus (arrow) in the same patient (fig. 1c). Capillaries in a normal mamillary body (arrows) (fig. 1d), light microscope, HE stain. Mamillary body in Wernicke's encephalopathy (fig. 1e), light microscope, HE stain. Fresh microhemorrhage, abnormal capillaries (arrow) and edematous neuropil (the same patient as in fig. 1b and 1c). Reactive astrocytes (stained brown) (fig. 1f, arrows), in mamillary body of the same patient, GFAP (glial fibrillary acidic protein) histochemistry.*

*When thiamine is transferred intracellularly, TDP is formed by the action af thiamine pyrophosphokinase. Magnesium is a vital cofactor of the enzyme and its activity corresponds to its concentration. In addition, the formation of active holoenzymes of TK, PDH and α-KGDH requires both TDP and magnesium for proper function, being composed of the apoenzymes of TK, PDH and α-KGDH, TDP and magnesium. Magnesium deficiency can reduce the proper binding of TDP to the apoenzymes, causing reduction in enzyme activity. In addition, animal studies have shown that increased concentration of magnesium reduces NMDA-receptor mediated excitotoxicity and severe deficiency increases it.

are 25-30 mg. Severe deficiency of thiamine develops in three weeks if ingestion shuts down.[25] Thiaminediphosphate (TDP) is the active form of intracellular thiamine. It is a vital cofactor of transketolase (TK), pyruvate dehydrogenase (PDH) and α-Ketoglutarate dehydrogenase (α-KGDH) that are key enzymes in glucose- and amino acid metabolism. Thiamine requirements increase with increased metabolic rate, e.g. in systemic infection.[25]

Chronic alcoholics have a lower ratio of thiamine in its active form of TDP and also a lower fractional increase of TDP after thiamine injections. Alcoholics with thiamine deficiency require therefore a higher dose of thiamine to respond similarly to normal controls[26] Furthermore, magnesium is a necessary cofactor in the formation of TDP and magnesium deficiency, common among alcoholics, appears to increase the neurological damage in thiamine deficiency*.[27-30] The response to thiamine treatment

can be inhibited by concurrent magnesium deficiency.[31-33] It may therefore be important to correct magnesium deficiency in addition to thiamine therapy in WE patients.

There are several reasons for the higher rate of WE in patients with chronic alcoholism. Nutritional deficiency with coexisting decrease in thiamine intake, vomiting or diarrhea are common in chronic alcoholism.[34] In malnourished individuals the ability of the gastrointestinal tract to absorb a fixed dose of thiamine is diminished and does not correct fully until after 6-8 weeks of a healthy nutritional diet.[35-37] The liver stores a large part of the body's supplies of thiamine and if diseased its capacity to store and handle thiamine diminishes.[34, 37, 38] Alcohol withdrawal, delirium tremens and infections all increase metabolic rate and requirements for thiamine.[1, 25] The formation of active thiamine requiring enzymes (TK, PDH and α-KGDH) is inhibited in alcoholics, due to the reduced utilization of thiamine (lower fraction of thiamine in the active form of TDP and magnesium deficiency). Chronic alcoholism causes up-regulation of NMDA-receptors that appears to increase the neurological damage in thiamine deficiency, through NMDA-receptor mediated excitotoxicity. [28, 29, 39]

Pathologic features

Histological changes in WE are of two main types: acute and chronic or permanent.

Acute changes are most frequently seen in the mamillary bodies, around the third and fourth ventricles and aqueduct of the midbrain. Specific changes in these areas are diagnostic of WE.[1,10] Punctate hemorrhages in the mamillary bodies (10%) or around the third ventricle are visible to the naked eye, but in 30% of cases the brain, including the mamillary bodies, has a normal macroscopic appearance[1, 10] (Figure 1a-1c). Microscopic examination is necessary for proper diagnosis and shows, almost without exception, symmetric histopathological changes in the mamillary bodies and most often in other areas as well, including the hypothalamus, thalamus (typically dorsomedial nuclei), around the aqueduct of the midbrain, in the oculomotor nuclei, nuclei dorsalis of the vagus, in the vestibular nuclei and the nuclei of the abducens nerves.[1, 10, 40] On microscopic examination acute vascular and neuropil changes predominate. Capillaries are pathologically prominent due to endothelial hypertrophy and possibly capillary proliferation. Edema, extravasation of red cells and microhemorrhages around capillaries are also

seen. Astrocytic reaction soon becomes prominent with destruction of myelin and axons, but reduction of nerve cells is seldom prominent in the mamillary bodies [1-3, 7, 10, 41] (Figure 1d-1f).

Permanent (chronic) changes are characterized by destruction of nerve tissue and gliosis in the areas mentioned above. Atrophy of the mamillary bodies is visible to the naked eye as well as widening of the third and fourth ventricles and the aqueduct of the midbrain. On microscopic examination there is proliferation of astrocytes, tissue destruction and gliosis. In the chronic histopathological changes of WE, the capillary endothelium appears normal and there are no pathologic fresh pericapillary hemorrhages. [1, 10, 40, 41] Chronic changes are often confined to the mamillary bodies and the dorsomedial nuclei of the thalami, opposed to acute changes that are typically found more widely, including the brain stem.[42]

Autopsy on individuals with the neuropathologic changes of WE often shows degeneration of the anterior-superior part of the cerebellar vermis. It is visible to the naked eye in slightly more than one third and in almost half on microscopic examination[1, 10] (Figure 2).

Clinical features

The clinical features of WE present acutely or subacutely (Table I). Its cardinal features are: 1) disorder of mental status or confusion, 2) oculomotor abnormalities and 3) stance and gait ataxia. Usually on examination only one or two of these cardinal features of WE are found and all three only in one third of the patients.[1]

Disorder of mental status: Most common is a global confusional state with lethargy and apathy, often without prominent agitation. Attention, concentration and memory are disturbed, and in more severe cases delerium tremens, stupor or coma are present.[1]

Oculomotor abnormality: Horizontal gaze evoked nystagmus is most common and many have vertical nystagmus as well. Also frequent are paresis or palsy of the ocular lateral rectus muscles (abducens nerves) and conjugate gaze paresis (dysconjugate gaze). Other less common ocular signs include: anisocoria, diminished pupillary reaction to light, retinal hemorrhages, ptosis, scotomata and papilledema.[1] 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.[43]
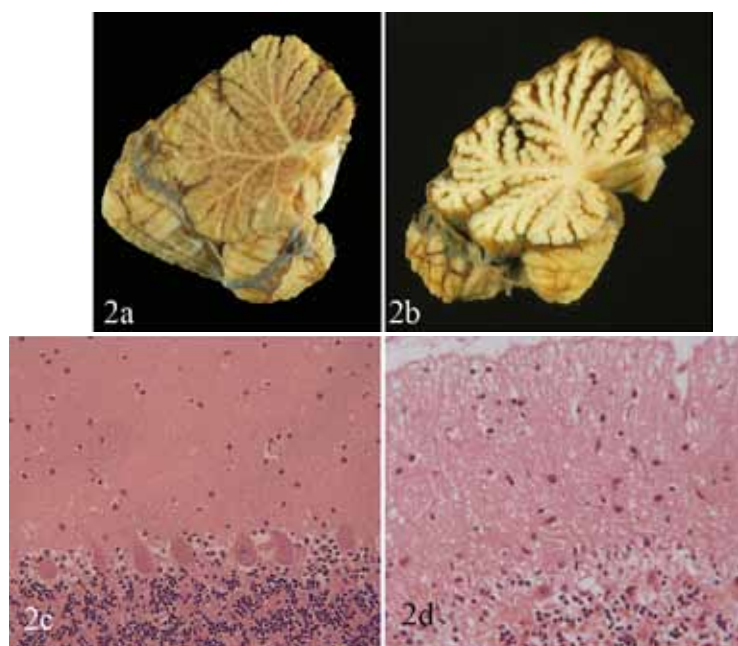
Figure 2: *Normal cerebellar vermis (fig. 2a). Significant atrophy of the cerebellar vermis (fig. 2b). Normal cerebellar cortex (fig. 2c), light microscope, HE stain. Atrophy and thinning of the cerebellar cortex. Purkinje cells are mostly gone, significant reduction in the number of granule cells and an increase in the number of glial cells in the molecular layer (fig. 2d).*

Table I: *Clinical features of Wernicke's encephalopathy.*

Clinical features or signs:	
Disorder of mental status	Global confusional state. Decreased level of consciousness, sometimes coma. Delerium tremens.
Oculomotor abnormalities	Horizontal or vertical nystagmus. Paresis or palsy of the ocular lateral rectus muscles (n. abducens). Conjugate gaze paresis (dysconjugate gaze). Less common signs: Anisocoria, diminished pupillary reaction to light, retinal hemorrhages, ptosis, scotomata, papilledema.
Stance and gait ataxia	Mild: abnormal tandem (heel-to-toe) walking Moderate: Wide based stance and a slow, shuffling, short stepped gait. Severe: Patient not able to stand or walk without support. Less common signs: Ataxia of legs, arms or speech.
Polyneuropathy	Acute or subacute polyneuropathy can be a sign of imminent Wernicke's encephalopathy. Loss of tendon reflexes, muscle weakness. Pain or sensory loss, usually begins in distal portions of the legs and then hands, with progression to proximal legs and arms.
Other and less common signs	Bilateral facial palsy. Bulbar palsy: dysphagia, dysarthria. Hoarseness and weakness of the voice. Hypothermia. Orthostatic hypotension. Urinary retention.

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-

Table II: *Clinical criteria for presumed Wernicke's encephalopathy. All patients with presumed WE should be treated with high doses of parenteral thiamine without delay.*

Diagnosis of a presumed Wernicke's encephalopathy among alcoholics requires both 1) and 2):

1) Evidence of chronic alcohol misuse

2) Any one of the following unexplained features:
   Acute confusion (not due to intoxication) or delirium tremens.
   Decreased conscious level.
   Memory disturbance.
   Opthalmoplegia, nystagmus.
   Ataxia (not due to intoxication) (*)
   Hypothermia with hypotension.

(*) It should be noted that the ataxia in acute WE is characterized by imbalance or ataxia on sitting up it bed, standing and walking, most likely due to acute bilateral vestibular dysfunction (that can be assessed by caloric testing), often with little or no ataxia in the extremities on heel-knee to shin testing or finger-nose testing.

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.[1]

In acute WE ataxia can be present in the extremities, most often seen on heel-knee to shin test but ataxic speech (scanning or slurred speech) is rare.[1] The imbalance when sitting, standing or walking is believed to be due to an acute dysfunction in the vestibular nuclei. Two studies have shown that a vestibular nuclear dysfunction is almost a universal finding in patients with acute WE. It can be confirmed by ice-water caloric testing, or similar tests, of vestibulo-ocular function. In WE there is a reduced or absent vestibulo-ocular response on ice-water irrigation of the ear-canal. After thiamine treatment and recovery from the acute phase the vestibule-ocular response can take up to two months to normalize.[44, 45] On the other hand, the chronic gait disturbance often present after recovery from acute WE (and commonly observed in chronic alcoholics without prior WE) is believed to be caused by degeneration of the cerebellar vermis (not by vestibular dysfunction).[1]

Polyneuropathy is seen among 60-82% of patients with WS, either affecting only the legs (57%) or both arms and legs (25%).[1, 46] Acute or subacute polyneuropathy can be seen early in or shortly before the presentation of WE.[4, 47] Korsakoff originally described polyneuropathy as a presenting feature, hence the name "psychosis polyneuritica".[4] 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 begin in the feet and can progress proximally, affecting fingers and hands and with continued progression 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 with urinary retention. Affection of the vagus nerve can cause dysphagia, hoarseness or weakness of the voice.[48]

Other less common signs: Hypothermia is rare (1-4%), believed to be due to a lesion in the posterior part of the hypothalamus.[1, 10, 49] Hypotension is seen among 2% of patients. Bilateral facial paresis, bulbar paresis[1] or extremity paresis with increased tendon reflexes and positive Babinski[50] are also rare.

Sequel of Wernicke's encephalopathy

If an individual with an acute WE does not receive thiamine through food or treatment, he will die. Even with treatment, permanent damage is common.[1] **Korsakoff´s amnestic syndrome (KS)** is a well known sequel of acute WE, characterized by difficulty in remembering events (episodic memory) prior to (retrograde amnesia) and following (anterograde amnesia) the acute illness. Patients with KS have diminished episodic memory and reduced ability to memorize or learn new things. They have little insight into and are indifferent to their disability and their initiative and spontaneity may be reduced to the point of apathy.[1, 4.] In the most comprehensive study of the acute treatment and sequel of WE to date, patients were treated with a much smaller dose of thiamine (50-100 mg daily), than is currently recommended (600-1500 mg daily). In this study the patients´ prospects were dismal, 24% died and 81% of the survivors developed KS.[1] The severity of their amnestic syndrome was varied and so were the degrees of memory function recovery during the first months after the illness. Recovery of memory function among patient with KS ranged from complete (21%), to significant (25%), slight (28%) or none (26%).[1] The majority were left with **a chronic gait disturbance** (62%), characterized by a slow, wide-based gait and abnormal performance on tandem walking.[1] Ocular paresis resolved soon after treatment with thiamine, recovery often starting within a few hours. **Nystagmus** improved more slowly and in 60% it was permanent.[1]

Diagnosis

The diagnosis of acute WE is frequently missed by physicians. One study showed that only 20% of cases were correctly diagnosed before death, although the great majority was evaluated by a physician in hospital shortly before dying.[51] In clinical studies only one third of the cases have all three main features of the disease[1] and in retrospective studies of pathologically diagnosed

cases only 16% have all three main clinical features of WE noted in their charts.[51]

There is a possible lack of proper neurological evaluation of alcoholics with WE, as disturbances of mental status are the most often recorded clinical features in the charts but features requiring more thorough neurologic evaluation like nystagmus, ataxia and gait disturbance are more seldom noted.[5, 6, 11, 51]

It is important for physicians to recognize the clinical features of WE and consider this diagnosis when chronic alcoholics present with confusion or gait disturbance. They should do a thorough neurological evaluation in the attempt to reveal the more specific signs of WE and keep in mind that only a minority of patients with WE have all the main clinical features of the disease at presentation. It is important to remember that some of the typical features of WE can easily be attributed to intoxication with alcohol or drugs, infection, electrolyte imbalance, etc.

Neurologic evaluation: Changes in mental status, such as decreased level of consciousness and disorientation should be noted. Particular attention should be paid to a presence of ocular muscle paresis or nystagmus and the patient's ability to sit up in bed, stand and walk normally and unaided, including tandem walking. After clinical evaluation ancillary tests should be ordered according to likely differential diagnoses and possible complications of WE. Serum concentration of magnesium should be ordered and there should be a low threshold for an acute CT brain scan. MRI of the brain with contrast should be ordered acutely or subacutely.

A presumptive diagnosis of WE: In 2001 The Royal College of Physicians published guidelines on the diagnosis and treatment of WE in accident and emergency departments.[52] Important additions to those are recommendations by Thomson and Marshall on the treatment of patients at risk of developing Wernicke's encephalopathy in the community.[53] Accordingly, only a presumptive diagnosis of WE (a presumed WE) is needed to treat patients immediately with high dose thiamine. Patients having a history or signs of chronic alcohol misuse and any of the following unexplained symptoms: Acute confusion (not due to intoxication), delirium tremens, memory disturbance, decreased conscious level, opthalmoplegia or nystagmus, ataxia (not due to intoxication) or unexplained hypothermia with hypotension should be presumed to have WE and treated accordingly. (Table II).[52, 53] It should be noted that the ataxia in WE is characterized by imbalance or ataxia on

Table III: *Operational criteria for the diagnosis of Wernicke's encephalopathy. Diagnosis of Wernicke's encephalopathy requires two of the following four signs:*

Clinical signs:	
Dietary deficiency	History of grossly impaired dietary intake. Body mass index lower than two SD below normal. Abnormal thiamine status on laboratory testing.
Oculomotor abnormalities (eye signs)	Opthalmoplegia. Nystagmus. Gaze palsy.
Cerebellar dysfunction (cerebellar signs)	Unsteadiness to sit, stand or walk (*). Ataxia or abnormalities on heel-knee to shin testing, past pointing or dysdiadokokinesis.
Altered mental state or mild memory impairment	Altered mental state: Confusion. Disorientation in two of three fields. Decreased level of consciousness - comatose. An abnormal digit span. Mild memory impairment: Failure to remember two or more words in the four item memory test. Impairment on neuropsychological tests of memory function.

(*) It should be noted that the imbalance in acute WE is most likely do to acute bilateral vestibular dysfunction (that can be assessed by caloric testing), but here it is classified under cerebellar dysfunction.

sitting up in bed or standing and walking and is most likely due to acute bilateral vestibular dysfunction, often with little or no ataxia in the extremities on heel-knee to shin testing or finger-nose testing.[1]

Caine et al. published **operational criteria for the diagnosis of WE and KS** (Wernicke-Korsakoff syndrome) among alcoholics in 1997 (Table III). Their purpose was to increase the precision of clinical diagnosis. According to them two out of the four following have to be present for diagnosis: 1) Dietary deficiency, 2) oculomotor abnormalities (eye signs), 3) cerebellar dysfunction (cerebellar signs) or 4) altered mental state or mild memory impairment. KS is diagnosed if the patient fulfills the criteria for WE and additionally has memory impairment and disorientation without being in a confusional state. In KS the patient has a normal level of consciousness and memory impairment does not resolve with thiamine treatment. It is noteworthy that the diagnostic criteria were validated retrospectively on 106 deceased alcoholic patients by reviewing charts and comparing them to neuropathologic results. The sensitivity of the criteria was 85% and specificity 100% in diagnosing WE and the sensitivity was 88% for diagnosing KS. Notably, the sensitivity was only 50% in diagnosing WE if there was a concurrent hepatic encephalopathy. The similarity of clinical features in patients with hepatic encephalopathy and WE is a likely explanation

Table IV: *Confirmation of a probable or presumed Wernicke's encephalopathy. Typical disease evolution, MRI changes or results of neuropathology can confirm the clinical diagnosis of a presumed Wernicke's encephalopathy. Importantly, all patients with presumed WE should be treated with high doses of parenteral thiamine without delay and the treatment should not be delayed for confirmation of the diagnosis.*

Confirmatory factors:	
Typical MRI changes in acute Wernicke's encephalopathy	Typical symmetric signal changes on MRI around the third ventricle, in the mammillary bodies, medial thalami or around the aqueduct of the midbrain.
Typical improvement of gaze palsy or nystagmus after thiamine treatment	Recovery of gaze palsy is usually complete within 10 days. Recovery of nystagmus can take up to 12 weeks and in some patients the nystagmus never recovers fully.
Typical neurological deficits in the course of acute illness	A new or worse persistent anterograde memory impairment (Korsakoff amnesic syndrome), stance and gait ataxia or nystagmus in the course of a presumed acute Wernicke's encephalopathy.
Typical degenerative brain changes on MRI in the course of WE	Few weeks to months after an acute Wernicke's encephalopathy, MRI can show significant atrophy of the mammillary bodies or cerebellar vermis, widening of the third ventricle or aqueduct of the midbrain.
Diagnostic neuropathologic changes	Neuropathology can show diagnostic acute or chronic histopathologic changes.

for the low sensitivity.[54] These diagnostic criteria have not been validated prospectively and they probably do not have high specificity in diagnosing acute WE from other causes of encephalopathy in alcoholics, particularly in alcoholics with chronic sequel, like nystagmus or gait disturbance, after prior episodes of WE or alcoholic cerebellar degeneration. The criteria's main strength, however, is ensuring that most patients with acute WE receive proper therapy and are therefore less likely to end up with disabling neurological sequel. Many patients will be given unnecessarily high doses of thiamine, but thiamine therapy is not costly and seldom has serious adverse effects.

Laboratory measurement of thiamine deficiency: Thiamine deficiency can be assessed by measuring the activity of transketolase (TK) in hemolysed blood. In thiamine deficiency the activity of TK is significantly diminished in the hemolysate and shows abnormal increase in enzyme activity (>25%) with the addition of a saturating dose of TDP (increased TDP effect).[55, 56] The concentration of thiamine, thiamine monophosphate and TDP can also be measured directly in blood or hemolysed erythrocytes with chromatography.[57] These methods have limited or no role in the clinical diagnosis of acute WE.

Magnetic resonance imaging (MRI): The diagnosis of WE is clinical, based on history, neurologic evaluation, response to thiamine treatment and characteristic evolution of the illness. MRI is of major importance for the diagnosis, especially if neurological expertise or neurological evaluation is limited or the disease presentation atypical. MRI may also reveal other possible causes of the symptoms.

The typical MRI changes in acute WE are symmetric signal changes (signal increasement on T2 weighted and decreasement on T1 weighted sequences) around the third ventricle, in the mamillary bodies, medial thalami and around the aqueduct of the midbrain (areas of neuropathological lesions).[50, 58, 59] Changes in these areas can also be discerned on FLAIR sequences or diffusion-weighted imaging[59, 60] (Figures 3-4). Contrast enhancement is seen among 63-67% of patients that have MRI changes in acute WE. It is most often limited to the mamillary bodies and is sometimes the only diagnostic change seen on MRI.[50, 59] In two studies on the role of MRI in the diagnosis of WE, sensitivity of MRI was 53-58% and specificity 93% in revealing changes corresponding to WE.[61, 62] Therefore, patients with acute WE commonly have a normal MRI which does not rule out a possible diagnosis of an acute WE.

Figure 3: *FLAIR sequence in axial and sagital planes shows signs of Wernicke's encephalopathy. Increased signal around the third ventricle and medially in both thalami (thick arrow). Also increased signal around the aqueduct of the midbrain (narrow arrow) and in the tectal plate (<). Mamillary bodies are smaller than normal (>).*
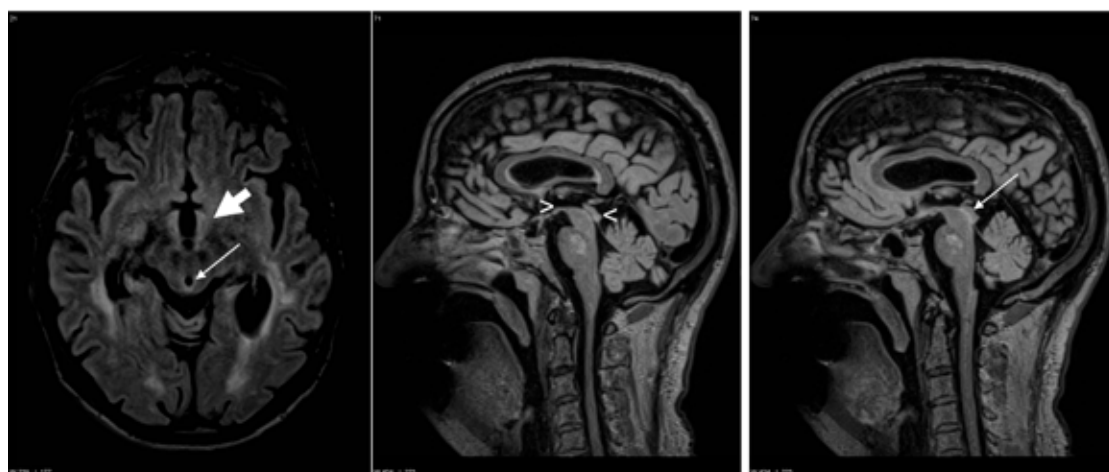
In the course of the illness (weeks to months), an MRI often shows degenerative changes in the brain (atrophy of the mamillary bodies, enlargement of the third ventricle or aqueduct and possibly degeneration of the cerebellar vermis) [63] (Figure 5). These changes, when seen on MRI during the illness can strongly support or confirm the clinical diagnosis of WE*.[64-68]

Confirmation of a presumed WE: It should be noted that response to thiamine, how the disease resolves, and possible neurological sequel are highly characteristic of WE and can be used in addition to possible changes on MRI or neuropathology to confirm the clinical diagnosis of a presumed WE (Table IV).

Differential diagnosis

Intoxication with alcohol or drugs can cause all the main features of WE. Some diseases can also be clinically similar to WE or KS, or may show similar changes on MRI, the most important being 1) Bilateral paramedian thalamic infarcts that can have similar clinical features as an acute WE [69-71], 2) anterior thalamic or mamillothalamic tract infarcts that can give similar clinical features as KS [69,72,73], 3) cytomegalovirus (CMV) encephalitis, well known in immunocompromised patients, especially in AIDS, can both have similar clinical features and show similar changes on MRI as an acute WE [74,75], 4) demyelinating diseases, neurological Behçet's disease and herpes (HSV) encephalitis are also possible differential diagnoses, 5) Hepatic encephalopathy can be difficult to distinguish clinically from an acute WE[54], especially among alcoholics that have had a prior episode or history of WE or alcoholic cerebellar degeneration, with chronic sequel of nystagmus or stance and gait ataxia.
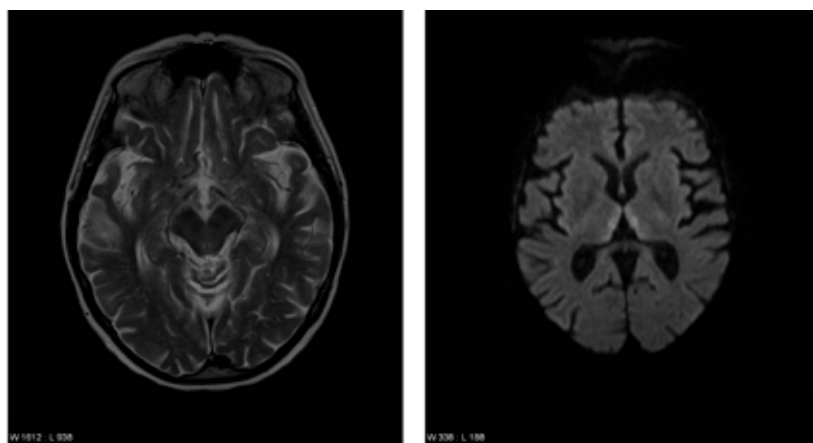

Figure 4: *T2 weigted image shows relatively small mamillary bodies (fig. 5A). Diffusion weighted image (DWI) demonstrates restricted diffusion of the medial thalami as high signal in the medial and posterior part of the thalamus on both sides (fig. 5B). Early diagnosis is essential in WE in order to avoid persistent brain damage. DWI has been shown to be the most sensitive method for imaging of early intracellular edema. DWI may lower the threshold for detection and is therefore a valuable imaging sequence in patients with suspected WE .*

Treatment of likely Wernicke's encephalopathy

All alcoholics with a likely WE should be treated with high doses of thiamine without delay. Included are alcoholics with a presumed acute WE (Table II and III), serious head injury or other conditions that make proper neurologic evaluation impossible, resulting in the inability to exclude the diagnosis of WE with reasonable confidence.[52] Physicians should also be alert to the possibility of acute WE in alcoholics with hepatic encephalopathy, even treat them with high doses of thiamine and assess their clinical response.[54] Thiamine should never be given by mouth in acute WE as the absorption of thiamine from the gastrointestinal tract in alcoholics is low and unpredictable. Thiamine should only be given intravenously or intramuscularly.[36,52,76]

Recommended thiamine treatment: There are no randomized controlled clinical trials or other reliable clinical studies on the critical

*The size and possible atrophy of the mamillary bodies can be assessed by measuring the volume of the mamillary bodies on MRI, using the equation: $V = 4/3 \, (a^2 b)$ where a is the shortest and b is the longest radius of the mamilary body. Normal combined volume in adults is 63.5 ± 17.6 mm³ but in the course of WE a significant atrophy or decrease in the volumes of the mamillary bodies can be seen, or: 24.3 ± 11.1 mm³, 21.3 ± 5.8 mm³ and 20.7 ± 14.8 mm³ according to three studies. Importantly, the mamillary bodies in chronic alcoholics that do not have neuropathological evidence of prior WE are not significantly smaller than among controls. Finally, the mamillary bodies are smaller than 23 mm³ among 64.5% of individuals in the course of WE, 2.3% of patients with chronic alcoholism without evidence of prior WE and only 1.2% of controls.
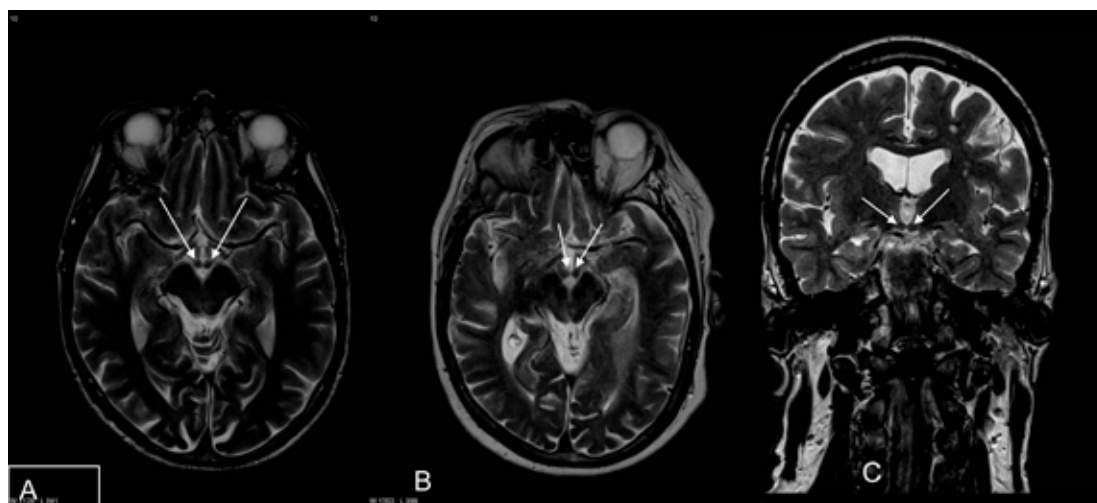
Figure 5: *Changes of the mamillary bodies in Wernicke-Korsakoff syndrome. Mamillary bodies can best be seen on T2 sequence pictures (fig. 4A). In acute Wernicke's encephalopathy a contrast enhancement in the mamillary bodies on T1 sequence pictures can be seen (not shown). Among patients with or after Wernicke's encephalopathy smaller mamillary bodies can be discerned (fig. 4B and 4C) in comparison to the mamillary bodies of healthy individuals (fig 4A).*

dose of thiamine needed to minimize disabling neurological outcome after acute WE.[77] Recent guidelines concerning the proper dose of thiamine in WE are founded on several factors, all of which support the use of much higher doses than have previously been given: 1) The knowledge of the dismal prospects for patients if treated with the lower doses (50-100 mg daily) previously used, 2) better knowledge of the pharmacodynamics of thiamine in thiamine deficient patients, 3) the differences in the pharmaodynamics of thiamine in alcoholics compared to non-alcoholics, 4) published cases and clinical experience (including our own experience of unpublished Icelandic cases) that point toward reduced neurological sequel following higher doses of thiamine and 5) low frequency of adverse effects with parenteral thiamine therapy. It should be noted that anaphylaxis is a very rare adverse effect when thiamine is given intravenously or intramuscularly.[35, 39, 52, 78-81]

Two guidelines have recently been published on treatment for acute WE. One recommends thiamine hydrochloride 500 mg given three times daily intravenously for three consecutive days. If the response is positive, the dose should then be lowered to 500 mg daily 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 sought.[52] The other recommends thiamine hydrochloride 200 mg given three times daily intravenously until there is no further improvement in signs and symptoms.[82] Thiamine hydrochloride can be administrated slowly intravenously[80, 81] but both guidelines recommend infusion of thiamine diluted with normal saline or 5% glucose given over 30 minutes.

Correction of magnesium deficiency with intravenous infusion of magnesium sulfate seems logical in acute WE as magnesium deficiency appears to increase the neurological damage in thiamine deficiency[27-30] and the response to thiamine treatment can be deficient in patients with significant magnesium deficiency.[31-33] Additional studies on the role of magnesium deficiency in WE and the neurological damage in chronic alcoholism seems a promising field for further studies. Correction of magnesium deficiency with oral therapy to minimize the damage in WE is inappropriate because of the high probability of absorption disturbance and the need for a rapid correction in acute WE. It takes several days of parenteral therapy to correct the intracellular magnesium deficiency.[83, 84]

Prophylactic therapy

Prophylactic thiamine should be given immediately on admission to all alcoholics with a significant risk of WE, including those needing medical detoxification, having evidence of nutritional deficiency or receiving intravenous glucose solution. Loss of appetite, nausea and vomiting can be the first signs of thiamine deficiency.[85] As discussed previously it is inappropriate to give admitted alcoholics oral thiamine to prevent WE. Thiamine hydrochloride 200-250 mg should be given daily for three to five days intramuscularly to minimize the risk of WE in admitted alcoholics.[53, 79, 86]

It is reasonable to recommend patients with active chronic alcoholism to take vitamin supplements containing at least 15 mg of thiamine daily. Thiamine supplementation can reduce the risk of their developing thiamine deficiency which causes many of the chronic disabling neurological complications of alcoholism.[1, 26] To increase compliance it is advisable to ask close relatives to buy the supplements or include them with other medicines in a medical dosing from a pharmacy.

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