

Nonalcoholic Wernicke's encephalopathy: a retrospective study of 17 cases

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Abstract

Objective: Nonalcoholic Wernicke's encephalopathy (WE) is a devastating neuropsychiatric syndrome caused by thiamine deficiency. Although many case reports on WE have been published, more studies are required to guide the diagnosis and treatment of nonalcoholic WE.

Methods: We retrospectively studied patients who were diagnosed with WE in our hospital. Data on demographics, possible causes, phenomenology, and diagnostic and treatment delays were abstracted from medical records by chart reviews.

Results: Seventeen patients were diagnosed with nonalcoholic WE. Nonalcoholic WE had many causes, such as gastrointestinal surgery, gastrointestinal tract diseases, vomiting, and psychiatric diseases. Most patients presented with abnormal mental symptoms, including those in a coma.

Conclusion: In summary, we recommend using operational criteria to diagnose and treat nonalcoholic WE as early as possible to avoid misdiagnosis and treatment delays. Nonalcoholic WE remains a clinical diagnosis, and certain examinations are helpful for this diagnosis, such as measuring serum thiamine concentrations. We should focus on patients who present with abnormal mental symptoms, even those in a coma, and administer parenteral thiamine before any carbohydrate to reduce the high frequency of residual morbidity.

Keywords

Nonalcoholic Wernicke's encephalopathy, thiamine deficiency, diet, eye signs, cerebellar dysfunction, Caine criteria

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Introduction

Nonalcoholic Wernicke's encephalopathy (WE) is a rare and devastating neurological pathology due to thiamine deficiency.¹ The concept of WE and Wernicke's triad originated with Carl Wernicke. This author described three patients in 1881 who presented with the classic triad of abnormal mental symptoms, dystaxia, and eye symptoms due to brain lesions discovered on autopsy.² Although WE is characterized by this clinical triad (abnormal mental symptoms, dystaxia, and eye symptoms³), these symptoms may not be apparent in some nonalcoholic patients with WE. However, the operationalized criteria proposed by Caine et al. in 1997 represent a diagnostic tool with much greater sensitivity than the classic triad. Additionally, some examinations are helpful in confirming a diagnosis of nonalcoholic WE. These examinations include brain magnetic resonance imaging (MRI),⁴ routine blood tests, blood thiamine assessments, and other ancillary investigations. These examinations should never delay treatment of nonalcoholic WE. Positive lesions of nonalcoholic WE on MRI, which are usually symmetrical, are mainly found in the medial thalami, mammillary bodies, tectal plate, and periaqueductal gray matter.⁵ Sometimes these lesions are found in the cerebellum, cranial nerve nuclei, and cerebral cortex.⁶ If the clinical triad of abnormal mental symptoms, dystaxia, and eye symptoms³ are not apparent in nonalcoholic patients with WE, MRI may confirm a diagnosis because of its high specificity. However, MRI has low sensitivity and could thus potentially delay treatment and should not be considered a major tool. An effective response to parenteral thiamine administration supports the diagnostic accuracy of nonalcoholic WE. Misdiagnosis and treatment delays for

nonalcoholic WE are common in clinical practice.⁷

Brain lesions are caused by thiamine deficiency in nonalcoholic patients with WE. Thiamine is an important co-enzyme for the pyruvate dehydrogenase complex, transketolase α -ketoglutarate, and the dehydrogenase complex, which are involved in glucose degradation and thus energy metabolism.^{6,7} Moreover, a deficiency of these enzymes caused by thiamine deficiency results in increased anaerobic fermentation and even lactic acidosis, causing permanent brain cell damage and ultimately death.⁸

We report our experience of patients with nonalcoholic WE in our hospital during the last 5 years. Our findings will be useful for reminding practicing clinicians to pay attention to this rare and serious neurological pathology.

Methods

Setting and study design

This study was designed as a retrospective chart review and was conducted at Yijishan Hospital in Anhui, China. The sample consisted of adult inpatients who were diagnosed with nonalcoholic WE between March 1 2013 and March 1 2018. Patients with WE caused by alcohol use were excluded.

The study protocol was approved by the hospital ethics committee of Wannan Medical College Affiliated with Yijishan Hospital. Informed consent was obtained from the patients.

Data analysis

All data analyses were performed using Microsoft Excel 2010 (Redmond, WA, USA). Descriptive statistics (means, standard deviations, frequencies, and percentages) were calculated for demographic

and medical variables, possible causes, phenomenology, diagnostic and treatment delays, and MRI data. Descriptive data were used to examine potential factors contributing to misdiagnosis and treatment delays for nonalcoholic WE.

Results

Demographics and medical variables

Nineteen patients were initially included, but two patients with WE caused by alcohol use were excluded. Therefore, 17 patients were included in our study. The patients' characteristics are shown in Table 1. The median age of the 17 patients was 52.18 years (mean: 52.18, range: 23–80 years) and 50% were men. Five (29.4%) patients were from the Neurology Department, six (35.3%) were from the Department of Critical Care Medicine, two (11.8%) were from the Gastroenterology Department, two (11.8%) were from the Emergency Room of Internal Medicine, and two (11.8%) were from the General Surgery Department.

Possible causes

The possible causes of WE are shown in Table 2. All patients (n=17; 100%) had at least one risk factor associated with decreased thiamine availability.

Phenomenology

The clinical manifestations of WE are shown in Table 3. The patients were grouped by symptoms, including abnormal mental symptoms, cerebellar dysfunction, gait ataxia, and eye symptoms. The most common symptom was a change in consciousness.

Diagnostic and treatment delays

All patients were diagnosed according to operational criteria proposed by Caine

Table 1. Demographics and medical variables of the 17 patients in Yijishan Hospital in Anhui, China.

Characteristic	Value
Male sex, n (%)	8 (47.1)
Age, years	
Median	52.18
Interquartile range	23–80
Age group, n (%)	
≤15 years	0 (0.0)
16–30 years	1 (5.9)
31–50 years	7 (41.2)
51–65 years	4 (23.5)
>65 years	5 (29.4)
Department, n (%)	
Critical Care Medicine	6 (35.3)
Neurology	5 (29.4)
Gastroenterology	2 (11.8)
Emergency Room of Internal Medicine	2 (11.8)
General Surgery	2 (11.8)
Pre-existing conditions, n (%)	
Hypertension	2 (11.8)
Pancreatitis	2 (11.8)
Cancer	3 (17.6)
Hypothyroidism	1 (5.9)
Cerebral infarction	1 (5.9)
Depressive disorder	1 (5.9)
Postoperative duodenal ulcer repair	1 (5.9)
MRI	13 (76.5)

MRI: magnetic resonance imaging.

Table 2. List of causes of Wernicke's encephalopathy.

Possible causes	n (%)
Dietary deficiencies	17 (100)
Gastrointestinal surgery	5 (29.4)
Gastrointestinal tract diseases	1 (5.9)
Vomiting	4 (23.5)
Pancreatitis	2 (11.8)
Psychiatric diseases	1 (5.9)
Others	2 (11.8)

et al.,⁹ which included malnutrition, abnormal mental symptoms, ataxia, and eye symptoms. All of the features defined in the operational criteria for diagnosing WE

Table 3. Signs and symptoms.

Signs and Symptoms	n (%)
Altered mental state or mild memory impairment	17 (100)
Cerebellar dysfunction	0 (0)
Eye signs	5 (29.4)
Gait ataxia	1 (5.9)

Table 4. Therapeutic course and effects.

Therapeutic course and effects	n (%)
Median time between onset of illness and treatment initiation (interquartile range), days	
Unrelieved patients	60.8 (4–270)
Relieved patients	3.9 (0–28)
Median time from treatment initiation to symptom resolution, days	
Unrelieved patients	No data available
Relieved patients	2.4 (0–7)
Hospitalization, n (%)	17 (100)
Length of stay (days)	
Unrelieved patients	36.8 (10–89)
Relieved patients	12.2 (1–42)

The term unrelieved means no relief from signs or symptoms and relieved means relief from signs or symptoms.

proposed by Caine et al.⁹ were present in all 17 cases in our study. A delay in therapy was calculated as the number of days between onset of symptoms and initiation of therapy. The median time from onset of illness to initiation of treatment was 3.9 days (0–28 days) in patients who had relief from signs or symptoms and 60.8 days (4–270 days) in patients who did not have relief from signs or symptoms (Table 4). In our study, two cases progressed to Wernicke–Korsakoff syndrome because of misdiagnoses and a delay in therapy.

MRI

Nonalcoholic WE is usually diagnosed clinically, but 13 patients underwent MRI to further confirm the diagnosis in our study. Positive manifestations of nonalcoholic WE were found on MRI in all 13 patients, which resulted in a positive rate of 100%. Seven patients had typical MRI manifestations of nonalcoholic WE (Figures 1–3). However, the other five patients did not show typical MRI findings of nonalcoholic WE. Symmetrical hyperintense signals were observed in the medial thalamus (6, 50%) and periaqueductal gray matter (4, 33.3%). Some patients also showed hyperintense signals at the level of the hippocampus (1, 8.3%), dorsal pons (2, 16.7%), cerebral

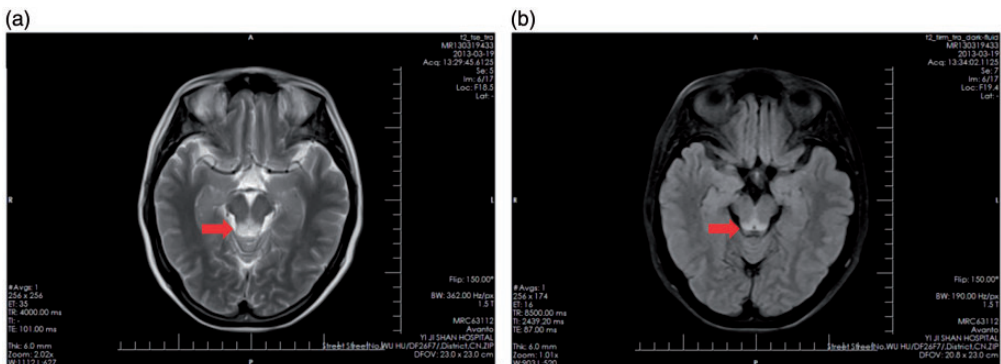


Figure 1. T2-weighted axial (a) and fluid-attenuated inversion-recovery coronal (b) images showing hyperintense signal alteration at the level of the periaqueductal gray matter.

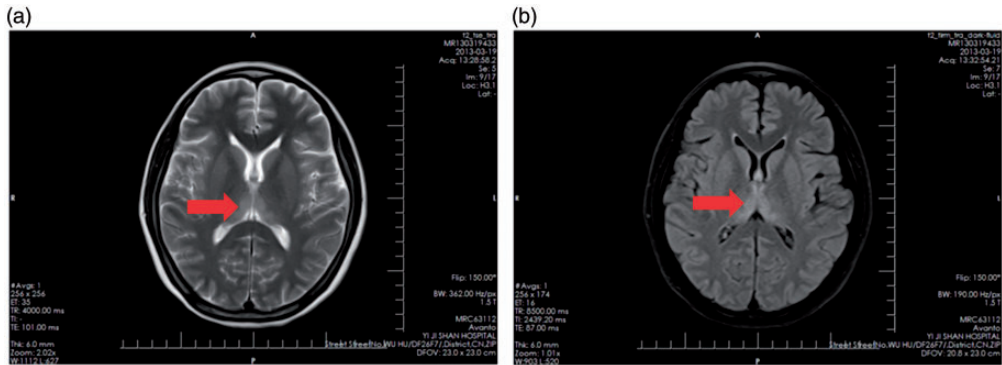


Figure 2. T2-weighted axial (a) and fluid-attenuated inversion-recovery coronal (b) images showing bilateral and symmetric hyperintense signal alteration at the level of the medial portion of the thalami.

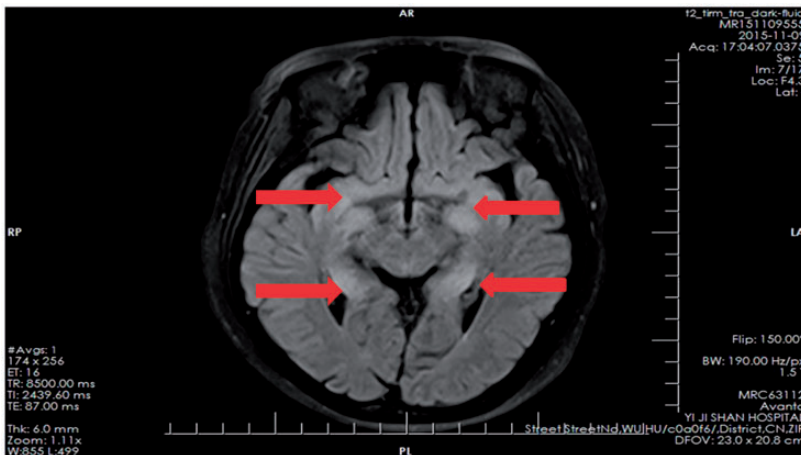


Figure 3. Fluid-attenuated inversion-recovery coronal images showing hyperintense signal alteration at the level of the medial portion of the thalami (a) and at the level around the hippocampus (b).

peduncle (1, 8.3%), basal ganglia region (1, 8.3%), and medulla oblongata (1, 8.3%).

Symptom resolution, clinical characteristics, and radiographic findings

Fourteen (82.4%) patients showed complete resolution of symptoms and the remaining three (17.6%) had residual symptoms. The median time between initiation of treatment and resolution of symptoms was 2.4 days (0–7 days) in patients who

had relief from signs or symptoms. No data were available for patients who did not have relief from signs or symptoms (Table 4).

Discussion

Nonalcoholic WE is a rare and extremely dangerous neurological pathology due to thiamine deficiency.¹ Thiamine is important for carbohydrate metabolism because it is a crucial cofactor for α -ketoglutarate

dehydrogenase, pyruvate dehydrogenase, and transketolase. Therefore, areas of the brain with high energy metabolism may be damaged because of excess accumulation of toxic intermediates, which is caused by thiamine deficiency.⁶ Therefore, thiamine is crucial for health.

Possible causes

The most common mechanism of nonalcoholic WE is decreased thiamine availability, which is caused by starvation, vomiting, and other factors. Consistent with other studies, dietary deficiencies were the most common cause of WE in this study. Malnutrition and decreasing thiamine absorption due to gastrointestinal surgeries are the most common causes of WE.¹⁰ In clinical practice, gastrointestinal surgery, gastrointestinal tract diseases, vomiting, pancreatitis, psychiatric diseases, and other risk factors may cause nonalcoholic WE. Dietary deficiency is usually related to gastrointestinal surgeries, which result in a poor appetite and can cause gastrointestinal absorption disorders. Gastrointestinal surgeries include gastrectomy and duodenectomy. Gastrointestinal surgeries are not related to thiamine deficiency. However, because gastrointestinal surgeries can result in poor appetite, dietary deficiency, and gastrointestinal absorption disorders, they can eventually indirectly cause thiamine deficiency. Notably, while vomiting can cause thiamine deficiency, it can also be a gastrointestinal manifestation of thiamine deficiency.¹¹

Phenomenology

In clinical practice, the most common clinical features of WE are abnormal mental symptoms. In our study, most patients had varying degrees of a change in consciousness.^{5,12,13} Ocular findings were

present in five cases, but none of the patients in our sample showed cerebellar signs.

Diagnostic and treatment delays

For clinical doctors, achieving an early diagnosis in WE remains a challenge. We diagnose a patient with nonalcoholic WE if the patient presents with two of the following signs: dietary deficiencies, eye signs, cerebellar dysfunction, and disturbance of consciousness.¹⁰ An initial diagnosis of nonalcoholic WE mainly relies on clinical symptoms because no specific laboratory tests are available.¹⁴ Because there are no specific routine laboratory tests for diagnosis of WE, the initial diagnosis of WE is based on clinical findings. Measuring blood thiamine concentrations or erythrocyte transketolase activity may be useful for diagnosing WE.⁶ The limitations of blood tests are that they are costly and time-consuming. However, because the prognosis of WE is favorable in patients who are diagnosed and treated early, early diagnosis and timely administration of thiamine is important.

MRI is an important examination for diagnosing nonalcoholic WE. MRI can show symmetric abnormalities in the periaqueductal gray matter, the tectal plate, the mammillary bodies, and the region surrounding the third ventricle, including the paramedian thalamic nuclei.¹⁵ High-intensity signals are often observed in the posteromedial thalamus or the area surrounding the third ventricle on diffusion-weighted images, T2-weighted sequences, and fluid-attenuated inversion-recovery images in patients with nonalcoholic WE.¹⁰ In our study of 17 patients, brain MRI was performed in 13 (76%) patients and seven (54%) had MRI manifestations typical of nonalcoholic WE. Isenberg-Grzeda reported a series of 18 cases in

which 30% of the patients had MRI manifestations typical of nonalcoholic WE.¹⁶

In clinical practice, most patients receive examinations that may not be helpful for diagnosing WE, some of which are costly, time-consuming, and invasive (e.g., lumbar puncture). As soon as nonalcoholic WE is suspected, therapy should be started. However, diagnostic delays were common in our study, which is consistent with the literature.⁶ The possible causes of a delay in diagnosis and treatment include doctors' lack of awareness of WE, delayed referral to a higher center, and late consultation with a neurologist. Because there is no specific routine laboratory test for diagnosing WE, the initial diagnosis of WE remains based on clinical findings.

In our study, misdiagnosis and delays in therapy occurred in some patients and even in one patient who was transferred from another hospital, with delay times as high as 20 days. The median time between the onset of illness and treatment initiation was 3.9 days (0–28 days) in patients who had relief from signs or symptoms and 60.8 days (4–270 days) in patients who did not have relief from signs or symptoms. Isenberg-Grzeda reported 18 patients with cancer and nonalcoholic Wernicke–Korsakoff syndrome who had an average delay of 18 days (range: 2–58 days).¹⁶ Delayed treatment is associated with a poor outcome of WE.¹⁷ Without prompt therapy, patients can develop a permanent disturbance of consciousness, even progressing to a coma, and they finally progress to Wernicke–Korsakoff syndrome.⁸ In our study, two cases progressed to Wernicke–Korsakoff syndrome.

Resolution of symptoms

Patients with suspected nonalcoholic WE require an immediate parenteral injection of thiamine. The recommended regimen is 500 or 200 mg of thiamine intravenously

infused three times daily.^{14,18} In summary, nonalcoholic WE is an extremely dangerous neuropsychiatric syndrome caused by thiamine deficiency. If diagnosed and treated promptly, nonalcoholic WE is easily resolved.^{19,20} Therefore, therapy should be started as early as possible to avoid permanent brain damage.²⁰ In clinical practice, some patients had residual abnormal cognitive symptoms, even a coma, because of misdiagnosis and therapy delays.

Treatment recommendations

The Caine criteria are a diagnostic tool with much greater sensitivity than has been recommended for the diagnosis of WE. Additionally, brain MRI, routine blood tests, blood thiamine assessments, and other ancillary investigations are helpful in confirming a diagnosis of nonalcoholic WE. If nonalcoholic WE is suspected, treatment should be initiated immediately.¹⁹ We recommend an injection of parenteral thiamine before any carbohydrate injection for all patients who present with abnormal mental symptoms, including a coma, with unknown causes. Treatment is based on parenteral thiamine therapy (vitamin B1).²¹

This study has several limitations. First, we only enrolled patients with nonalcoholic WE. Therefore, we cannot discuss the difference between patients with alcoholic and nonalcoholic WE. Chronic alcoholism is the main cause of alcoholic WE, but importantly, many other conditions can be responsible for nonalcoholic WE. Second, the present study had a retrospective design and lacked randomization. Therefore, data abstraction could not be blinded. For determining the pathogenesis of and treatment for WE, studies with larger samples and a prospective design are required. Third, we did not examine the effect of treatment delays in WE on long-term prognoses. In the clinical setting, WE is easily misdiagnosed, and this can

result in disabling dysfunction, with a mortality rate of 20% in delayed cases.¹⁰

Conclusions

The study was based on real cases of non-alcoholic WE from our hospital. Although the results of our study are partly consistent with those of previous studies, because of the severe consequences of misdiagnosis and treatment delays for WE, our findings suggest the following. We should diagnose nonalcoholic WE promptly and parenteral thiamine should be injected before any carbohydrate injection for all patients who present with abnormal mental symptoms, even a coma, with unknown causes. Nonalcoholic WE remains a clinical diagnosis. However, significant advances in imaging and laboratory assessments have been achieved for diagnosing nonalcoholic WE.

List of abbreviations

WE: Wernicke's encephalopathy.
MRI: magnetic resonance imaging.

Authors' contributions

All authors met the authorship criteria and participated in this study. Hongzhen Yin, MD, Tao Yu, MD, PhD, and Weihua Lu, MD were involved in the conception and design; Hongzhen Yin, MD, Qiancheng Xu, MD, Yingya Cao, MD, Yupeng Qi, MD, and Tao Yu, MD, PhD were involved in acquisition of patients; Hongzhen Yin performed statistical analysis; Hongzhen Yin, MD, Qiancheng Xu, MD, and Yupeng Qi acquired, analyzed, and interpreted the data; Hongzhen Yin, MD wrote the article; and Tao Yu critically revised the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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