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Case report

Wernicke Encephalopathy: Late-Stage Symptoms

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SUMMARY

Introduction. Wernicke encephalopathy is a rare acute/subacute neurological disorder, commonly caused by prolonged thiamine deficiency in patients who chronically consume alcohol. According to the Caine classification criteria, the clinical diagnosis of this encephalopathy involves at least two of the following four signs: nutritional deficiency, oculomotor dysfunction, ataxia, and changes in the mental status. This case report highlights rare clinical signs in the late stage of the disease, as well as the consequences of possible local hypoperfusion of the brainstem in the form of an ischemic vascular event.
Case report. A 39-year-old female patient (previously treated at a regional general hospital) was admitted to the Department of Emergency Neurology at the University Clinical Center of Vojvodina with a history of a series of epileptic seizures, altered consciousness, oculomotor signs, opisthotonus, and cognitive dysfunction, following years of alcohol consumption and nutritional deficiency. The diagnosis was confirmed by typical neuroimaging findings and specific laboratory tests. Hypertonia with subsequent opisthotonus was one of the clinical manifestations in our patient, while the occurrence of an ischemic stroke was an unexpected event. Empirical administration of high-dose thiamine, along with additional supportive intensive therapy, did not yield satisfactory outcomes.
Conclusion. Wernicke encephalopathy represents a clinical diagnosis based on physical and neurological examination, with neuroimaging. Early recognition of both common and unusual symptoms, particularly in the late stage of the disease, could potentially reduce morbidity and mortality. It is essential to administer thiamine before glucose infusion to all patients with an undetermined cause of altered consciousness.

Keywords: **thiamine, Wernicke encephalopathy, alcoholism, opisthotonus, stroke**

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INTRODUCTION

Wernicke encephalopathy (WE) is a rare, devastating acute or subacute neurological disorder caused by prolonged thiamine (vitamin B1) deficiency. The prevalence of WE in different neuropathological studies varies between 0.4-2.8%, up to 12.5% in chronic alcoholic patients (1). Alcoholics are particularly predisposed to thiamine deficiency due to the low thiamine absorption rate at the mucosal level, the impaired hepatic function, and the alcohol-related raised thiamine metabolism (1-3). In addition, different clinical conditions can impair the correct absorption of thiamine: gastrointestinal surgery, prolonged vomiting, chemotherapy, systemic infectious and non-infectious diseases, and dietary imbalance (4).

According to the new Caine's classification criteria, clinical diagnosis of WE in alcoholics requires two of the following four signs: nutritional deficiency, ocular findings, ataxia, and mental status changes (5). To make a WE diagnosis promptly, Sechi and Serra have classified clinical symptoms and signs into three groups: symptoms common at presentation, uncommon at presentation, and late-stage symptoms (3). In this case report, we wanted to point out rare clinical signs in the late stage of the disease as well as the occurrence of stroke in WE and raise the awareness of this condition among adults.

CASE REPORT

A 39-year-old woman was admitted to Department of Emergency Neurology in an altered state of consciousness (Glasgow Coma Score 4), with myotic and non-reactive pupils, she had hypertonia with hyperexcitability of the myotatic stretch reflexes. On examination, she had stable vitals, albeit with pyrexia (38 °C), she was moderately underweight (BMI 17.9), tachycardic, and hypotensive. During the two weeks prior the admission, she had been hospitalized on Internal Medicine Department of a regional hospital due to hepatic dysfunction, deficit of albumin, folic acid, vitamins D and B12, electrolyte imbalance, and series of epileptic seizures. During that period, substitution therapy was started along with continuous infusions of glucose, and after that the working diagnosis of WE was established. From her past medical records, we found that she had the history of alcohol abuse for the past eight years, her food intake in the previous year was significantly decreased, and she demonstrated apathy with mild memory impairment for the past two years.

Upon admission to a tertiary healthcare facility, laboratory tests revealed mild alkalosis with pH 7.52, lactates were 0.9 (0.5-1.6 mmol/L), bicarbonates were elevated at 27.8 (22-26 mmol/L), blood magnesium was decreased at 0.47 (0.7-0.95 mmol/L) as well as blood potassium level at 2.8 (3.5-5.5 mmol/L), while levels of blood glucose (5.7 mmol/L), blood urea nitrogen (2.5 mmol/L) and blood creatinine (45 μmol/L) were within the reference range. Serum inflammation markers were elevated, with C-reactive protein (CRP) 87.3 mg/L (normal value is < 5 mg/L), and procalcitonin (PCT) level was 0.7 (normal value is < 0.1 ng/mL).

From the first day of hospitalization in our department, we registered transitory abnormal backward arching of the neck and body due to the severe muscle spasm (opistotonus) which lasted up to a few minutes, several times per day, with continuously present muscle hypertonia. The chest X-ray taken on admission demonstrated inflammation on the left side, which could explain the elevated CRP levels. Liver ultrasound revealed the signs of steatosis with coarse and fine-grained echostructure, while subsequent CT scan of the abdomen showed unevenly reduced density, particularly in the right lobe, with perfusion impairment, without clear focal changes. A moderate increase in liver enzymes (aspartate aminotransferase-73 (5-34 U/L), gamma-glutamyl transferase-228 (11-59 U/L)) was detected along with macrocytosis within chronic liver disease. Serum vitamin D < 11 (50-150 nmol/L) and folate 6.45 (8.6-45.3 nmol/L) levels were low, ammonium level was 13 (9.9-30 μmol/L), while the coagulation panel was unremarkable. The results of virologic workup, including tests for hepatitis A, B, C, D and E virus, human immunodeficiency virus (HIV) and cytomegalovirus (CMV), were unremarkable, too. The results of lumbar puncture and thyroid hormone levels were within normal limits. In all immunological analyses, the levels of antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti-smooth muscle antibodies (SMA) and anti-parietal cell antibodies (APCA), antinuclear antibody HEp-2, anti-transglutaminase IgA antibody (TGA-IgA), rheumatoid factor (RF) were measured; complements C3

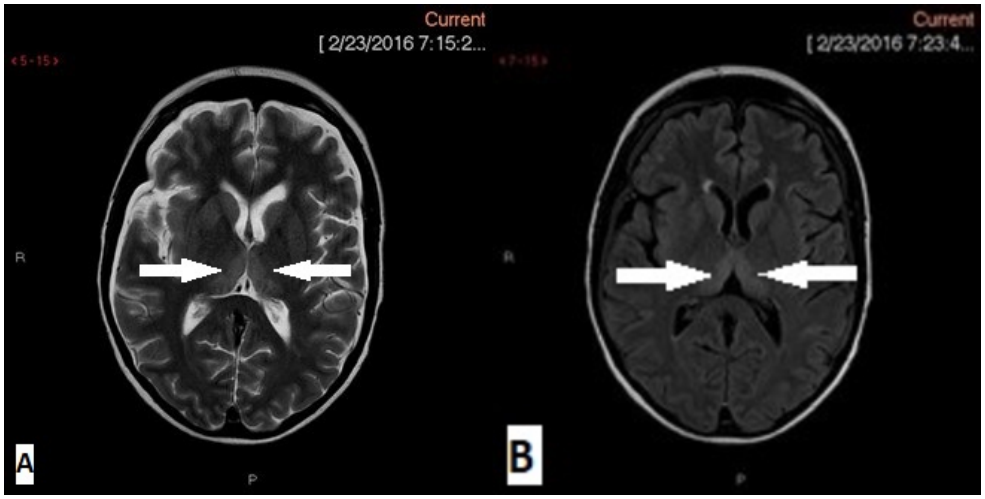

Figure 1. *(A, B): Axial T2-weighted/FLAIR images show symmetrically increased signal intensity in the dorsomedial thalami*

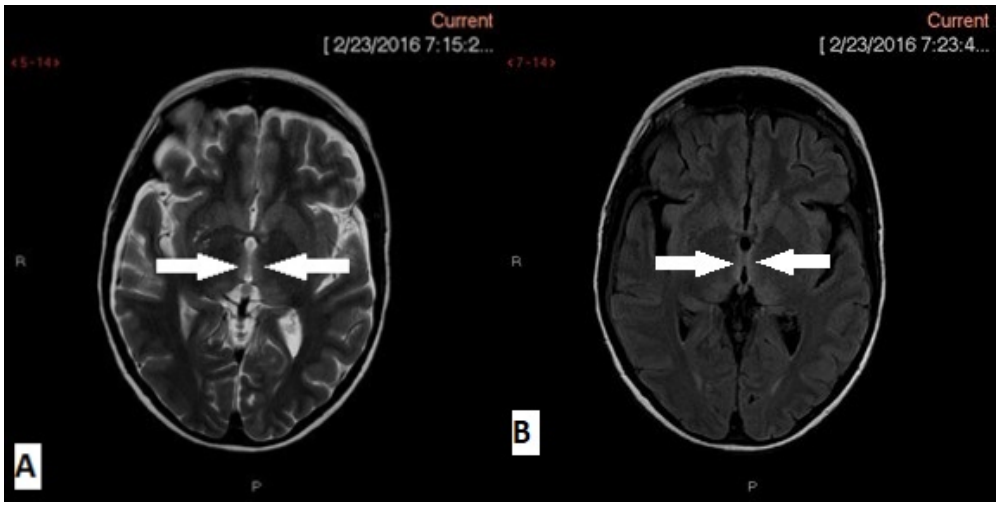

Figure 2. (A, B): *Axial T2-weighted/FLAIR images show symmetrically increased signal intensity in the periventricular region of the third ventricle*

and C4 were negative. Serum copper and ceruloplasmin levels were normal. A subsequent non-contrast CT brain scan was normal. On the fifth day of hospitalization, a brain MRI scan showed a symmetrical, hyperintense T2 signal in the region of dorsomedial thalami (Figure 1. (A,B) and around the third ventricle (Figure 2. A,B), as well as acute ischemic lesion of the pons (Figure 3. A,B). Electroencephalography (EEG) recording showed encephalopathic findings (Figure 4.).

During the initial period of hospitalization, the serum level of thiamine could not be determined due to technical issues. On the third day, we empirically started its intravenous administration in the three daily doses of 300 mg, combined with hepatoprotective and multivitamin therapy. After 24 hours, she improved dramatically, from a state of coma to obeying commands and opening her eyes appropriately. On the seventh day since the thiamine therapy began, we determined the serum normal range levels of 85 μg/L (28-85 μg/L).

In the following days, we registered only partial regression of neurological deficit, and the patient was conscious to somnolent, without verbal response and convulsions, having persisting muscle hypertonia with transient nuchal and lower spine rigidity, together with meanwhile registered horizontal nystagmus. After 12 days, the patient was transferred for further treatment to the secondary

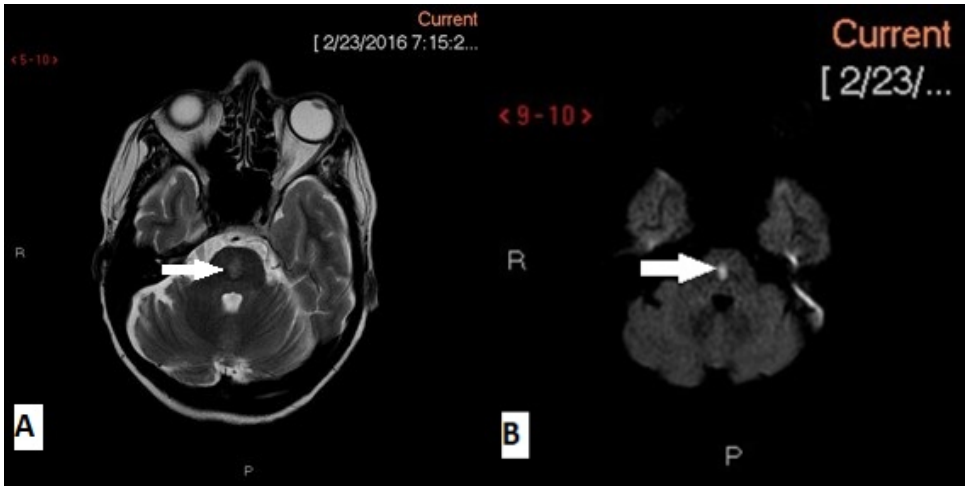

Figure 3. *(A, B): Axial T2-weighted/DWI images show minor high T2 and diffusion restriction abnormality in the central pons*

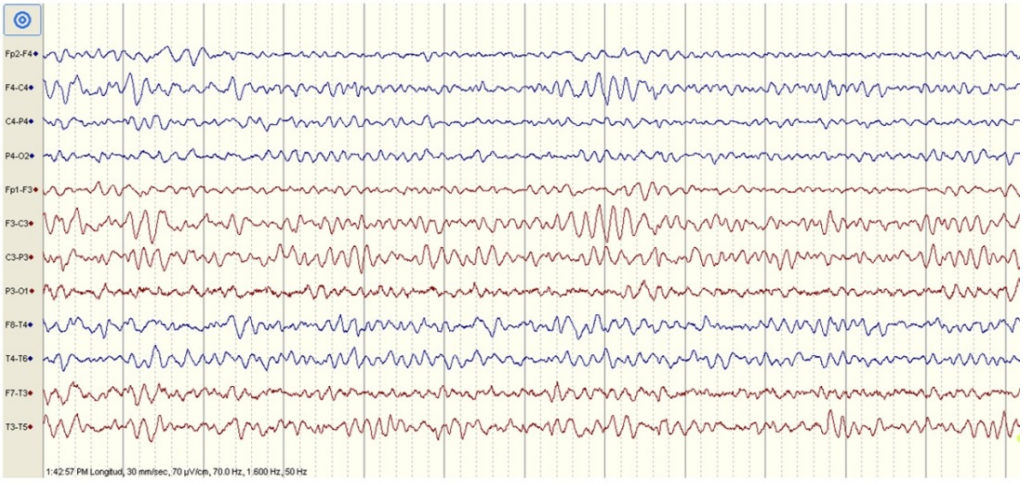

Figure 4. *The EEG shows moderate electrocortical dysrhythmia above bilateral centroparietal region, most prominent over the left side (calibration: 1 second/30 mm, 10 μV/mm)*

hospital care, where she died two weeks later. An autopsy was not performed.

Despite the lack of knowledge about temporal progression of neurological signs of WE, common symptoms (ocular abnormalities, mental status changes, incoordination of gait, and trunk ataxia) and uncommon symptoms or signs at presentation (hypotension and tachycardia, hypothermia, bilateral visual disturbances and papilledema, hearing loss, hallucinations, and behavioral disturbances) were established. Quantitative deterioration of consciousness (coma) is a hallmark of the late stage of disease (2-3 weeks after the onset of first symptoms) (3). A comatose state was described in the situations of untimely recognition of this disease and parenteral nutrition or glucose infusions without thiamine supplementation (which occurred in our patient) (6).

It has been considered that prolonged glucose administration without the addition of thiamine can be a risk factor for the clinical worsening in WE. The proposed underlining mechanism is that glucose activates glycolysis in which thiamine is consumed, which decreases its body supplies. At the cellular level, increase of lactates in the lesioned brain areas is due to anaerobic oxidation and lack of thiamine, along with underlying parenteral glucose administration. That is why the administration of glucose

before thiamine is not recommended (6, 7). On the other hand, Schabelman and Kuo, in reviewing the case reports, did not determine a clear influence of glucose infusions on the occurrence and deterioration of WE. A different methodological approach in a few case reports these authors analyzed was a limiting factor for the definite conclusion (8). In this case, our patient received protracted glucose infusions while being normoglycemic and without thiamine supplementation, while she was hospitalized in a regional medical center, which taken together could support previously mentioned hypothesis.

In the late phase of WE, patients can have seizures, hyperthermia caused by involvement of anterior hypothalamic regions, spastic paresis secondary to involvement of motor cortex or pyramidal tracts, hypertonia with nuchal and lower-spine rigidity, and choreic dyskinesias caused by damage to structures at mesopontine tegmentum (3). In our case, partial explanation of hypertonia could be found in the work of Zhang and colleagues who stated that the loss of neurons of anteroventral/ventrolateral (AVVL) and ventral posterolateral (VPL) thalamic nuclei, in the first hour from the beginning of epileptic seizures, could be responsible for hypertonia and opistotonus. In the next few hours, massive neuronal cell loss occurs in areas of other thalamic nuclei and mammillary bodies as well as in periaqueductal gray matter and in tegmentum of pons (9). According to other authors, a neuropathological mechanism of postural muscle tone loss would include metabolically caused structural lesions of mesopontine tegmental area and its reticular formation. Disfunction of dorsal reticulospinal tract causes disinhibition of the spinal cord which leads to hyperexcitability in opistotonus (3, 10). In our patient, MRI brain scan did not show lesions in this location of the brainstem, which does not exclude the existence of a lesion which could possibly be seen on MR spectroscopy or in postmortem examination.

Given that thiamine plays a key role in maintaining normal cellular and metabolic function in the brain, its deficiency leads to disruption of important enzyme pathways, increasing the vulnerability of the CNS (11). Specific places for neuronal damage are the ones with the highest need for thiamine such as gray matter of mamillary bodies, anterior and medial thalamic nuclei, upper and lower colliculi, and periventricular gray matter (12). As per literature, frequent histological changes can be found in bilateral, dorsal medial areas of thalamus as well (13). In our patient, we registered bilateral thalami and periventricular lesions, which pointed to brain structural selectivity and was in accord with the literature. The possible consequence of clinical or subclinical thiamine deficiency in alcoholism may contribute to significant variability in the range of alcoholism-related brain abnormalities detected. Possible explanations for this variability include individual alcohol use pattern (quantity, frequency, duration) and nutrition or hypothesis that different brain regions have different susceptibility to alcohol toxic effects, especially in the periventricular region where the blood-brain barrier is naturally thinner (4, 14, 15).

Another rarity relates to the ischemic pontine lesion detected in our patient. In the acute phase vascular congestion, microglial proliferation and petechial bleeding can be registered in WE, was a consequence of arteriolar and capillary dilatation (16), while the association of ischemia in WE has not been recorded in the literature frequently. Although ischemic stroke is not frequently described as a direct complication of Wernicke encephalopathy (17), certain mechanisms may explain this possible correlation. Namely, thiamine deficiency in WE leads to metabolic disturbances that can impair neuronal energy metabolism, particularly in structures such as the mammillary bodies, thalamus, and brainstem, which may increase the susceptibility of brain tissue to ischemic events. Moreover, patients with chronic alcoholism often have risk factors for ischemic stroke, including hypertension, cardiac arrhythmias, and coagulation disorders which can increase the likelihood of brain ischemic events.

Therefore, it is important to identify and appropriately manage all associated risk factors for cerebrovascular diseases in patients with Wernicke encephalopathy to reduce the likelihood of ischemic stroke.

CONCLUSION

Wernicke encephalopathy represents a clinical diagnosis which is based on physical and neurological examination along with neuroimaging. Apart from the already defined diagnostic criteria, in some cases, diagnosis of WE can be hard to establish due to rare and unrecognized clinical manifestations of this disease, such as muscle hypertonia and opistotonus. Using more detailed neuroimaging techniques such as functional MRI, contrast MRI, posi-

tron emission tomography and MR spectroscopy can allow physicians to examine both structural and functional changes that occur in patients with WE. With early recognition of frequent and unusual symptoms, especially in the late phase of disease, we can decrease morbidity, irreversible neurological damage or even death outcome, following the most important therapeutical guideline: thiamine should be given before glucose infusion to all patients with undetermined cause of comatose state.

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Authorship contributions: Conceptualization – ALP, VG; Data analysis – ALP, TKZ, VŽ; Writing – ALP, VG; Supervision – ALP. All authors read and approved of the final version of the manuscript.

Conflict of interest

The authors have no relevant financial or non-financial interest to disclose.

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Simptomi kasne faze Vernikeove encefalopatije

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S A Ž E T A K

Uvod. Vernikeova encefalopatija je redak akutni/subakutni neurološki poremećaj koji je najčešće uzrokovan prolongiranom deficijencijom tiamina kod osoba koje hronično konzumiraju alkohol. Prema Kejnovim klasifikacionim kriterijumima, klinička dijagnoza ove encefalopatije podrazumeva najmanje dva od sledeća četiri znaka: nutritivna deficijencija, okulomotorna disfunkcija, ataksija i promene mentalnog statusa. Pojava različitih kliničkih simptoma i znakova može biti uslovljena i razvojem bolesti. Ovaj prikaz ukazuje na retke kliničke znakove u kasnoj fazi bolesti, kao i na posledice moguće lokalne hipoperfuzije moždanog stabla u vidu ishemijskog vaskularnog događaja.
Prikaz slučaja. Tridesetdevetogodišnja bolesnica (prethodno lečena u regionalnoj opštoj bolnici) primljena je na Odeljenje urgentne neurologije Univerzitetskog kliničkog centra Vojvodine sa podacima o seriji epileptičnih napada, poremećaju svesti, pojavi okulomotornih znakova, opistotonusu i kognitivnoj disfunkciji. Bolesnica je godinama konzumirala alkohol i bila u stanju nutritivne deficijencije. Dijagnoza je potvrđena tipičnim neuroimidžing nalazom i specifičnim laboratorijskim pretragama. Hipertonija i posledični opistotonus su kliničke manifestacije Vernikeove encefalopatije, dok je ishemijski moždani udar bio neočekivana pojava. Empirijska primena visokih doza tiamina uz dodatnu potpornu intenzivnu terapiju dovela do zadovoljavajućeg ishoda.
Zaključak. Vernikeova encefalopatija predstavlja kliničku dijagnozu koja se temelji na fizičkom i neurološkom pregledu uz neuroimidžing. Rano prepoznavanje kako čestih, tako i neuobičajenih simptoma, posebno u kasnoj fazi bolesti, moglo bi uticati na smanjenje morbiditeta i smrtnog ishoda. Neophodno je slediti važnu terapijsku smernicu: tiamin treba ordinirati pre infuzije rastvora glukoze svim bolesnicima sa neutvrđenim uzrokom promenjenog stanja svesti.

Ključne reči: **tiamin, Vernikeova encefalopatija, alkoholizam, opistotonus, moždani udar**