Case report / Artykuł kazuistyczny

Undiagnosed Wernicke's encephalopathy. A case report on hyperactive delirium

Nierozpoznana encefalopatia Wernickego. Opis przypadku majaczenia hiperaktywnego

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Abstract

Introduction: Wernicke-Korsakoff syndrome can present with persistent altered mental status, delirium and agitation. The cause of Wernicke's encephalopathy (WE) is primary loss of thiamine in the mammillary bodies of the limbic area of the brain. WE can be seen in nearly 3% of the general population and studies show prevalence ranging from 13 to 60% in patients with alcohol abuse. Furthermore, it is often clinically under-recognised and thiamine treatment tends to be underutilised in at-risk patients.

Case description: We present a male in his 70s with a past medical history significant for alcohol use disorder who was admitted to hospital for acute metabolic encephalopathy and dizziness. At the physical exam, the patient was noted as having slurred speech, poor short- and long-term memory and horizontal nystagmus with fixed and frequent upward gaze. Hospital treatment was complicated by repeated aggression despite a negative neurologi-

Streszczenie

Wprowadzenie: Zespół Wernickego-Korsakowa może objawiać się trwałymi zmianami stanu psychicznego, majaczeniem i pobudzeniem. Encefalopatia Wernickego (*Wernicke's encephalopathy* – WE) jest pierwotnie spowodowana utratą tiaminy w ciałach suteczkowatych obszaru limbicznego mózgu. Zaburzenie to można potwierdzić u prawie 3% populacji generalnej, a wśród osób z diagnozą nadużywania alkoholu rozpowszechnienie waha się według różnych badań od 13 do 60%. Co więcej, WE jest zbyt rzadko rozpoznawana klinicznie, a leczenie tiaminą niedostatecznie wykorzystywane u pacjentów z podejrzeniem wystąpienia WE.

Opis przypadku: Przedstawiamy mężczyznę w wieku 70 lat, u którego w przeszłości rozpoznano zaburzenia spowodowane używaniem alkoholu. Został przyjęty do szpitala z powodu ostrej encefalopatii metabolicznej i zawrotów głowy. W badaniu stwierdzono niewyraźną mowę, słabą pamięć krótko- i długotrwałą oraz oczopląs

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cal and medical check-up. WE was diagnosed after several days of hospitalisation. The patient improved slowly after multiple weeks of parenteral thiamine supplementation.

Commentary: WE is a medical emergency and if left untreated or treated inappropriately, may result in a life-threatening and irreversible neurological damage and function impairment. While parenteral thiamine is the treatment mainstay for WE, there is little consensus on best dosage, duration or route. The following case report summarises the literature on best treatment for WE. Additional research needs to be conducted on biases leading to misdiagnosis of WE and best treatment regimens for thiamine supplementation.

Keywords: Thiamine, Wernicke-Korsakoff Syndrome, Wernicke Encephalopathy, Thiamine Deficiency.

poziomy ze wzrokiem nieruchomym i częstym spoglądaniem w górę. Przebieg leczenia szpitalnego był zakłócony przez powtarzające się akty agresji, której przyczyny nie można było ustalić, mimo przeprowadzanych badań lekarskich, w tym neurologicznych. WE zdiagnozowano dopiero po kilku dniach hospitalizacji. Po wielu tygodniach pozajelitowej suplementacji tiaminą stan pacjenta powoli się poprawiał.

Komentarz: Encefalopatia Wernickego jest ostrym stanem medycznym i nieleczona lub niewłaściwie leczona może zagrażać życiu oraz skutkować nieodwracalnymi zmianami neurologicznymi i upośledzeniem funkcji życiowych. Chociaż podanie pozajelitowe tiaminy jest główną metodą leczenia WE, to jednak nie ma pełnej zgody co do wielkości dawki oraz czasu i drogi jej podawania. W tym opisie przypadku podsumowano literaturę dotyczącą najlepszych metod leczenia WE. Konieczne są dodatkowe badania nad przyczynami błędnych diagnoz WE i najlepszymi schematami leczenia suplementacją tiaminy.

Słowa kluczowe: tiamina, syndrom Wernickego-Korsakowa, encefalopatia Wernickego, niedobór tiaminy.

Introduction

Wernicke's encephalopathy (WE) is an acute, possibly reversible state primarily due to loss of thiamine in the mammillary bodies of the limbic region as well as the thalamus, hypothalamus, and periaqueductal areas of the brain. WE can be observed in nearly 3% of the general population in the Western World and studies show prevalence ranging from 13 to 60% in patients with significant alcohol use [1, 2]. However, it should be considered that there has been limited data and research completed within recent years to reflect updated prevalence of WE. WE can sometimes be confused with alcohol intoxication or withdrawal or head injury due to the mental confusion, gait ataxia and ophthalmoplegia triad of classic symptoms. Consequently, the similarity in alcohol abuse patients' clinical presentation can make it difficult to diagnose and is often clinically under-recognised, resulting in underutilised thiamine treatments in at-risk patients. WE is a medical emergency and, if left untreated or treated inappropriately with either low doses of thiamine or oral thiamine, it may result in life-threatening and irreversible neurological damage and functional impairment known as Korsakoff syndrome (KS). The progression of untreated WE to the chronic phase of disease known as KS is also termed as "Wernicke-Korsakoff" syndrome (WKS). While parenteral thiamine is the mainstay of treatment for Wernicke's encephalopathy, there is little consensus on best dosage, duration or route. The following article presents a patient diagnosed with Wernicke's encephalopathy and summarises the literature on best treatment for WE.

Case description

We present the case of a male in his 70s with a medical history significant for alcohol use disorder, hypertension, chronic obstructive pulmonary disorder and cerebrovascular accident in 2019, who was admitted to hospital with dizziness and his treatment was complicated by alcohol with-

drawal and worsening altered mental status with agitation.

Additionally, a history of alcohol abuse, between 4-12 cans of beer daily, reduced in frequency to one to two beers daily two months ago, was revealed. Further information provided revealed recent changes in his behaviour including lack of interest in engaging with family, becoming less sociable overall and easily angered, raising his voice and using vulgar language, which was reportedly out of character. The patient has had also poor oral intake and had stopped eating over the past two weeks. Collateral endorsed worsened behaviour patterns with increased irritability over the past few months and strange eye movements over the past week, which worsened over the past two days. On interview, the patient lacked insight into his condition demonstrated by not being able to recount the events leading to his hospitalisation and to identify his current condition. Throughout the interview, the patient appears to be disoriented and was uncooperative with psychiatric evaluation, stating that he only wanted to rest and sleep. Upon further questioning, the patient demonstrated intermittent verbal agitation, often yelling at staff that he wanted to exit the room. The patient also demonstrated impaired short term memory as he was unable to recall his treatment team and medical recommendations throughout his hospital stay despite having a consistent care team.

At the physical exam, the patient was irritable and could not tolerate interview questions. The patient was oriented to people, but not time or place. Speech was low in volume and slightly slurred with poor intonation. His thought process was goal directed, there were no overt delusions expressed, and short term memory was impaired as demonstrated by being unable to recall either medical recommendations or his care team. According to collateral information prior to the examination, the patient was seen reaching out for items that were not physically present though there were no overt observed or reported internal auditory or visual stimuli during the hospital stay. Patient denies suicidal and homicidal ideation. Horizontal nystagmus with fixed gaze and frequent upward gaze were noted at the examination. Computed tomography (CT) and magnetic resonance imaging (MRI) showed white matter disease most consistent with chronic small vessel ischemic change, and chronic right occipital lobe infarct without evidence of acute infarct or haemorrhage.

The consulting psychiatry team diagnosed WE. The clinical triad of confusion, ataxia, and ocular motor dysfunction was observed as demonstrated by collateral information that the patient had acutely unsteady gait on admission, disorientation and impaired attention at the mental status exam and during interview, and nystagmus and frequent upward gaze observed at the physical exam. There is also significant concern about malnutrition given that the patient had been refusing oral intake for twelve days. Thiamine 500 mg intravenous (IV) three times per day for three days was completed and continued on thiamine 250 mg IV. The patient was also started on Mirtazapine 15 mg *per os* nightly for appetite and sleep and Depakote sprinkles 125 mg every 8 hours as needed for agitation. Supportive therapy and reassurance were provided and the patient continued to be monitored by psychiatry, neurology and the primary medicine team.

Throughout the patient's hospital course, the psychiatry team continued to see the patient daily to monitor signs and symptoms of WE. Patient tolerated psychiatric medications without any reported side effects. The patient self-reported that sleep and appetite continued to improve while in hospital. Hospital staff reported that the patient's behaviour was improving overall, demonstrating less lability and psychomotor agitation overall. After three days of high dose IV thiamine, the neurology team documented they were unable to appreciate the previously observed nystagmus at the neurological exam.

■ Commentary

Thiamine, also known as vitamin B_1, is an essential vitamin that plays an important role in the proliferation of cellular energy from ingested food. The human body is unable to produce thiamine, therefore it must be obtained within the diet and can be found in breads, cereals, meats, among other foods [3]. Once ingested, thiamine is absorbed in the duodenum and then converted into thiamine pyrophosphate [4], its active form. This process requires magnesium as cofactor [3]. Absorption is completed through a carrier-mediated process that can be decreased by the use of alcohol due to alteration in the expression of receptors

required for thiamine absorption [5]. Depending on the blood concentration of thiamine, transport across the blood-brain barrier can be either passive or active. Higher concentrations are transported by passive diffusion, while lower concentrations diffuse via active transport.

Thiamine deficiency occurs due to poor intake of vitamin-rich foods, impaired intestinal absorption, decreased liver storage capacity or alcohol-induced kidney damage and excessive loss associated with medical conditions [6]. Insufficient intake of thiamine leads to decreased activity of thiamine-dependent enzymes causing a compromise in cell respiration. Cell, specifically neuron, necrosis occurs as these have high thiamine demand and metabolic requirement. Studies have shown that cell death occurs in several areas of the brain including the thalamus, hippocampus, cerebellum, pons, brain regions around the ventricles and a few cortical areas [7, 8]. WE is a common neuropsychiatric syndrome that can be a result of alcohol-induced thiamine deficiency, commonly manifesting in those who have been diagnosed with alcohol-use disorder [9]. This has been known to be a main cause of WE in western countries, however, WE has also been identified in patients with malabsorption, malnutrition, gastrointestinal malignancies, dialysis, hyperemesis gravidarum, AIDS and bariatric surgery [10]. WE is classically known to present with the triad of gait ataxia, mental status changes and ophthalmoplegia. Nevertheless, this classic triad is present in only a fraction, with one study indicating less than a third, of cases making it difficult to distinguish between intoxication of alcohol, benzodiazepine withdrawal, sepsis, hypoxia, hypomagnesaemia and hepatic encephalopathy. Clinical diagnosis has been shown to be missing in up to 80% of cases [11].

WE is a medical emergency and if left untreated or treated inappropriately with either low doses of thiamine or oral thiamine, it may result in a life-threatening situation. Known as Wernicke-Korsakoff syndrome (WKS) or Korsakoff syndrome (KS), it is characterised by symptoms of opthalmoplegia, ataxia, acute confusion, unexplained hypotension, confabulations, memory disturbance, hypothermia and unconsciousness [6]. If WE is diagnosed early and treated appropriately, the symptoms can be reversed. However, if it progresses to KS, it has become a chronic condition characterised as irreversible. One study by Arts *et al.* concluded that there is currently no effective pharmacological treatment of KS, and emphasised the need to diagnose and treat WE adequately before it progresses [12]. Due to WE being largely caused by alcohol consumption, oral replacement of thiamine has been shown not to be an adequate treatment plan due to the reduced intestinal thiamine absorption [10]. Thiamine replacement, intravenously or intramuscularly, is the standard treatment. However, a consensus on optimal dose, frequency and duration has yet to be established [13, 14]. Several studies suggest using a high dose of IV thiamine treatment (500 mg) three times a day for 3-5 days to facilitate diffusion across the blood-brain barrier and restore vitamin status [13]. This is then is followed by an oral regimen of 250-1000 mg of thiamine until alcohol reduction or abstinence [15]. One study completed by Nakamura *et al.* illustrated that a high IV dose regimen was associated with a decrease in mortality [16]. Despite differences in recommendations in treatment and prevention for WE between clinicians, all have established that a high suspicion for WE warrants aggressive treatment in order to prevent a life-threatening situation in the clinical setting along with the high benefit-to-risk ratio of high dose thiamine.

Conflict of interest/Konflikt interesów

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Ethics/Etyka

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) on medical research involving human subjects, Uniform Requirements for manuscripts submitted to biomedical journals and the ethical principles defined in the Farmington Consensus of 1997.

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