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**CASE REPORT**

# Wernicke encephalopathy without delirium in patients with cancer

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## ABSTRACT

*Objective:* Wernicke encephalopathy (WE) is a neuropsychiatric disorder caused by thiamine deficiency. Several reports of WE in cancer patients are known. WE is sometimes overlooked because most patients do not exhibit its typical symptoms (e.g., delirium, ataxia, ocular palsy). If delirium is not present, a diagnosis of WE is difficult because delirium is the hallmark symptom of WE.

*Method:* Taken from a series on WE in cancer, we report two patients who developed WE without delirium during periodic psycho-oncology outpatient visits.

*Results:* **Case 1**. A 61-year-old woman with non-Hodgkin lymphoma who was periodically attending a psycho-oncology outpatient clinic developed an unsteady gait. WE was suspected because she also developed appetite loss for two weeks, and we could find no other laboratory findings to explain her unsteady gait. Our diagnosis was supported by abnormal serum thiamine and disappearance of the gait disturbance after intravenous thiamine administration. **Case 2**. A 50-year-old woman with breast carcinoma with bone metastasis developed an unsteady gait. WE was suspected because she also developed loss of appetite for two weeks, and no other laboratory findings could explain her unsteady gait. The diagnosis was supported by abnormal serum thiamine and disappearance of the gait disturbance after administration of intravenous thiamine.

*Significance of Results:* Our report emphasizes the importance of being aware of WE, even when patients do not present with delirium. The presence of loss of appetite for more than two weeks may be the key to a diagnosis of WE.

**KEYWORDS:** Wernicke encephalopathy, Delirium, Cancer, Thiamine deficiency, Vitamin B1

## INTRODUCTION

Wernicke encephalopathy (WE) is a neuropsychiatric disorder caused by a deficiency of thiamine (vitamin B1), which is necessary for oxidative metabolism (Hoyumpa, 1980; Manzo et al., 1994). This disorder is reversible if properly diagnosed and treated with thiamine supplementation. However, it is often unrecognized (Isenberg-Grzeda et al., 2016*b*). The main reason for underdiagnosis is the diversity of its symptoms (Isenberg-Grzeda et al., 2012).

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The classical symptoms of WE include delirium, ataxia, and opthalmoplegia; however, these symptoms are not specific to WE, and only 16% of autopsy samples and 11% of clinical cases exhibit these three symptoms; in addition, 19% of autopsy samples show none of the three (Harper et al., 1986; Isenberg-Grzeda et al., 2016*a*). However, if left untreated, it causes severe and irreversible brain damage (Korsakoff syndrome), leading to death.

The best aid for diagnosis of WE, particularly in patients with cancer, is clinical suspicion (Sechi et al., 2016).

Recent studies have revealed that WE patients with cancer are recognized in several situations during cancer progression (Isenberg-Grzeda et al., 2016*a*; Onishi et al., 2016; 2004). Most of the clinical cases of WE are recognized when patients develop delirium, but little is known about the clinical features of WE without delirium.

In this report, we identify cancer patients with WE and without delirium. Correct diagnosis and subsequent parenteral thiamine administration relieved their symptoms and prevented them from developing delirium and irreversible brain damage (Korsakoff syndrome).

## CASE REPORTS

### Case 1

A 61-year-old woman with non-Hodgkin lymphoma was referred by her hematological oncologist to the psycho-oncology outpatient clinic because of anxiety and depression. She was diagnosed with non-Hodgkin lymphoma 14 months previous and received chemotherapy and radiotherapy; however, her disease progressed. She continued chemotherapy.

On her first psychiatric examination, she exhibited anxiety about her prognosis. She could not accept her situation with respect to the disease. She also sometimes developed emotional incontinence.

She was a retired kindergarten teacher who was very kind to others and had no medical history of psychiatric illness, and she had not abused alcohol or drugs.

Her psychiatric features fulfilled the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM–V) (American Psychiatric Association, 2013) criteria for adjustment disorder with mixed anxiety and depression.

She was treated mainly with individual and group psychotherapy, which reduced her anxiety and depression. She also received chemotherapy and radiotherapy; however, her disease progressed.

Some 12 months after the first consultation at the psycho-oncology outpatient clinic, she visited our outpatient clinic using a wheelchair because of an unsteady gait. She said that she could not keep her feet firmly on the ground. She had been treated with 1150 mg of gemcitabine and 6.6 mg of dexamethasone 5 days before.

Neurological examination was unremarkable except for unsteadiness of gait. Delirium, headache, vomiting, nausea, and hemiparesis were not recognized.

She was 151 cm in height and weighed 48.8 kg (standard body weight = 50.56 kg).

Chest X-ray demonstrated no significant findings. Laboratory findings revealed that her aspartate aminotransferase, $\gamma$-glutamyltransferase, and glucose levels were elevated. She had received blood transfusions the day before. We could not find any laboratory findings to explain her unsteadiness.

A detailed interview with her and her husband revealed that she had developed loss of appetite more than two weeks earlier. Her husband reported that her appetite was 10% of normal for those 10 days and 50% of normal the week before that.

We suspected thiamine deficiency because ingested thiamine is stored in the body for approximately 18 days (MacLean et al., 1983). Furthermore, she developed loss of appetite more than 2 weeks previous, and unsteadiness of gait is one of the clinical signs of thiamine deficiency. We administered 100 mg of thiamine intravenously. Two days after thiamine administration, she could walk into the consultation room, and delirium was not observed. Anemia and liver dysfunction remained almost the same after thiamine administration.

Her serum thiamine level measured using high-performance liquid chromatography was 19 ng/ml (reference range = 24–66 ng/ml).

From these findings, she was diagnosed with WE without delirium.

### Case 2

A 45-year-old woman with breast carcinoma was referred by her oncologist to the psycho-oncology outpatient clinic because of anxiety. She had been diagnosed with breast carcinoma with bone metastasis 3 weeks before.

At the first psychiatric examination, she reported that she was anxious about the treatment and her future life. She had also developed a loss of interest. She had no past medical history of alcohol or drug abuse, and she was usually very kind to others.

Her psychiatric features fulfilled the DSM–V criteria (American Psychiatric Association, 2013) for adjustment disorder with anxiety. She was given psychotherapy, which reduced her anxiety. As for the breast cancer, she was treated with hormonal therapy and chemotherapy.

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Five years after the first consultation, she complained of unsteadiness of gait. She stated that she could not walk without the help of a cane. Neurological examination was negative except for unsteadiness of gait. Delirium, headache, and nausea and vomiting were not exhibited.

Two weeks previous, she began taking 120 mg of a TS-1 combination capsule (tegaful, gimeracil, and oteracil potassium) and 2 mg of eribulin.

She was 157 cm in height and her body weight was 64.7 kg (standard body weight = 53.5 kg).

Laboratory findings revealed that her aspartate aminotransferase, alkaline phosphatase, and lactate dehydrogenase values were elevated, but these could not explain her symptoms. A detailed interview with the patient revealed that she had developed loss of appetite and was eating 30% of normal for the past 2 weeks.

We suspected thiamine deficiency because she had developed loss of appetite for two weeks and body storage of thiamine deficiency is approximately 18 days, and because no other cause for the delirium was evident.

We administered 100 mg of thiamine intravenously. Several days after thiamine administration, she could walk without the help of a cane. Her serum thiamine level as measured using high-performance liquid chromatography was 23 ng/ml (reference range = 24–66 ng/ml). Neuroradiological studies revealed no brain metastasis.

From these findings, she was diagnosed with WE without delirium.

## DISCUSSION

We have identified two cases of WE who presented with ataxia as the sole neurological symptom. Although these patients did not develop delirium, clinical suspicion, early detection, and immediate parenteral thiamine administration had prevented development of delirium and Korsakoff syndrome. WE is a medical emergency because the patient can sustain irreversible brain damage, leading to death, if early diagnosis fails. Therefore, clinical suspicion and early detection are particularly important. However, early detection of subclinical thiamine deficiency is a difficult task (Sechi & Serra, 2007). The clinical course, symptoms, and signs presented for our two cases are useful for clinical suspicion and early detection in other new cases.

There are several reasons why WE without delirium is difficult to recognize. First, delirium is considered as the hallmark of WE. Therefore, most oncologists do not have a clinical suspicion of WE when delirium is not present. Second, all of the clinical symptoms of WE, even the classical triad, are not disease-specific. Chemotherapy-induced peripheral neuropathy is a common side effect of cancer treatment. The resulting sensory and motor dysfunction often leads to such functional impairments as gait or balance disorders (Kneis et al., 2016). Unsteadiness is not regarded as a symptom of WE if not accompanied by delirium. This may lead to underrecognition of WE.

The clue to the diagnosis of WE in these two cases was loss of appetite for about 2 weeks. Although the body stores thiamine for 18 days (MacLean et al., 1983), a decreased capacity for thiamine storage has been recognized in cancer patients (Onishi et al., 2005; Yae et al., 2005). It may be better to check thiamine deficiency in cancer patients, especially in advanced stages, if appetite loss has lasted for at least 2 weeks.

In an autopsy study (Harper et al., 1986), 19% of patients with WE had no documented clinical signs; in fact, only one patient was diagnosed with WE prior to death. Careful clinical observation should be able to reveal WE cases without the classical clinical triad.

In conclusion, we identified two cancer patients with WE without delirium. Careful clinical observation, including level and duration of loss of appetite, will be the key clue to clinical suspicion, early detection, and prevention of thiamine deficiency.

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