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Thiamine deficiency in the bereaved after cancer-related spousal loss

Hideki Onishi, M.D., PH.D.[1], Nozomu Uchida, M.D.[2], Takao Takahashi, M.D., PH.D.[3], Daisuke Furuya, M.D., PH.D.[4], Yasuhiro Ebihara, M.D., PH.D.[5], Izumi Sato, M.P.H., PH.D.[6], Hiroshi Ito, M.D.[7] and Mayumi Ishida, C.P., PH.D.[1]

[1]Department of Psycho-oncology, Saitama Medical University International Medical Center, Saitama, Japan; [2]Department of General Medicine, Ogano Town Central Hospital, Saitama, Japan; [3]Department of Supportive Medicine, Saitama Medical University International Medical Center, Saitama, Japan; [4]Department of General Medicine, Saitama Medical University International Medical Center, Saitama, Japan; [5]Department of Laboratory Medicine, Saitama Medical University International Medical Center, Saitama, Japan; [6]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan and [7]Ito Internal Medicine and Pediatric Clinic, Fukuoka, Japan

Case Report

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Author for correspondence:
Hideki Onishi, Department of Psycho-oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka City, Saitama 350-1298, Japan. Email: honishi@saitama-med.ac.jp

Abstract

Objective. Thiamine deficiency (TD) is recognized in various kinds of disease with associated loss of appetite including cancer. However, it has not been recognized to date in bereaved partners after spousal loss from cancer.

Method. From a series of bereaved partners who lost a spouse to cancer, we report on those who developed TD after bereavement.

Result. Case 1 was a 57-year-old woman who sought consultation at our "bereavement clinic." Her husband had been diagnosed with pancreatic cancer one year earlier and had died one month previously. At the first visit, she was observed to suffer depression, anxiety, and decreased appetite. Neurological, blood, and biochemical examinations did not reveal any noteworthy findings. She was diagnosed with uncomplicated bereavement. Detailed examination revealed that her appetite had been markedly decreased for approximately five weeks. The diagnosis of TD was supported by her abnormally low serum thiamine level. Case 2 was a bereaved 73-year-old male who had lost his wife to hypopharyngeal cancer one month previously after a five-year illness. He had shown a lack of energy for the month preceding his wife's death, but because there was no improvement after her death, his family recommended he seek consultation at our "bereavement clinic." He was suffering from major depressive disorder. Detailed examination revealed that his appetite had been decreased for more than two weeks. Again, the diagnosis of TD was supported by his abnormally low serum thiamine level.

Significance of results. These reports demonstrate that there is a possibility that bereaved could develop TD after the loss of a loved one. TD should be considered whenever there is a loss of appetite lasting for more than 2 weeks, and medical staff should pay careful attention to the physical condition of the bereaved to prevent complications because of TD.

Introduction

Bereavement is life's greatest stressor (Holmes & Rahe, 1967) and can influence the psychological, physical, and social aspects of the survivor' life. For example, in psychological terms, there are increases in the incidence of depression (Zisook & Shuchter, 1991) and suicide rate (Erlangsen et al., 2004; Kaprio et al., 1987; Li, 1995), whereas in physical terms, an increase in the mortality rate from cardiovascular disease (Carey et al., 2014) has been reported.

Based on such findings, we established a "bereavement clinic" at our institution to treat and provide care for bereaved family members, and we have reported various findings related to the medical treatment of the psychological, physical, and social aspects of bereavement (Ishida et al., 2010, 2011, 2012, 2015, 2018).

Thiamine, in its biologically active form, thiamine pyrophosphate, is an essential coenzyme for oxidative metabolism (Sechi et al., 2016b). However, because it cannot be synthesized in vivo, maintenance of an appropriate level depends on ingestion from outside the body. The stores of thiamine in the body can be depleted in as little as 18 days (MacLean et al., 1983), and serum thiamine concentration declines with a reduction in dietary intake lasting two to three weeks (Sechi et al., 2016b).

Thiamine deficiency typically leads to the disease known as Wernicke's encephalopathy (WE). This disease presents with a wide spectrum of signs and symptoms, ranging from cognitive, mood, or behavioral changes, through to ocular, cerebellar, and other neurologic signs. The presentation is quite heterogeneous, and the historical concept of a "triad" of symptoms is no longer recognized as clinically valid. Treatment consists of the administration of thiamine,

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and if the disease is identified and treated in the early stage it can be resolved without sequelae. However, these symptoms are nonspecific, and less than 20% of cases present with all three symptoms. Further, the disease is often confused with other neuropsychiatric symptoms, and is often overlooked (Isenberg-Grzeda et al., 2012). If overlooked long term, it can progress to Korsakoff syndrome, leading to severe brain-related complications. The subsequent mortality rate is high at 17% (Victor et al., 1971).

Recent studies have shown that cancer patients can develop thiamine deficiency, with the timing of onset ranging from preoperative to end-stage and presenting a diverse range of symptoms (Onishi et al., 2016, 2018a, 2018b, 2018c, 2018d, 2018e, 2018f; Isenberg-Grzeda et al., 2015, 2016a, 2016b, 2017; Sechi et al., 2016a). Furthermore, thiamine deficiencies have also been recognized in family members caring for cancer patients (Onishi et al., 2019).

Here we report two cases of thiamine deficiency in the bereaved after cancer-related spousal loss who visited our "bereavement clinic." In both cases, the onset of WE was prevented by timely treatment.

Case Report

Case 1

A 57-year-old woman visited our "bereavement clinic" for a consultation on the advice of a physician from the Department of Supportive Therapy at our institution.

Her husband had been diagnosed with pancreatic cancer with liver metastasis one year earlier, and despite undergoing chemotherapy and radiation therapy, the disease progressed and he had died one month before her visit.

The bereaved consulted the bereavement clinic because she continued to experience anxiety and regret following her husband's death. Her psychological symptoms at the first visit included depression, anxiety, and decreased appetite. In addition, she felt regret regarding choices made in relation to treatment options and place of care.

No neurological symptoms such as disturbed consciousness, ataxia, or ocular symptoms were observed. No findings of note were observed on her blood and biochemical examinations.

She had no medical history of psychiatric illness or alcohol or drug abuse. Her psychiatric features fulfilled the criteria set out in *The Diagnostic and Statistical Manual of Mental Disorders 5th edition* (American Psychiatric Association, 2013) for uncomplicated bereavement.

More detailed examination revealed a decrease in appetite to about 30% of normal that had continued from approximately one week before her husband had died. Because thiamine is stored in the body for as little as 18 days, we considered the possibility of thiamine deficiency and 100 mg of thiamine was intravenously injected after collection of a blood sample to test her blood thiamine level. After five days, it was revealed that her blood thiamine level had decreased to 23 ng/mL (reference range: 24–66 ng/mL). However, there was no onset of WE.

Case 2

A 73-year-old male was brought for a consultation at our "bereavement clinic" by his daughter.

His wife had suffered from hypopharyngeal cancer for five years. Despite treatment, her symptoms progressed and she died one month before his visit.

He had shown a lack of energy for the month preceding his wife's death, but because there was no improvement after her death his family became concerned and recommended he seek consultation.

Psychiatric consultation at the initial visit revealed depression, decreased motivation, decreased appetite, sleep disturbance, inhibition, and difficulty concentrating. Neurological examination showed no disturbance of consciousness, ataxia, or ocular symptoms.

Normal blood and biochemical examinations did not show any notable abnormalities, and computed tomography scans of the head did not reveal anything of note. He had no medical history of psychiatric illness, or alcohol or drug abuse. His psychiatric features fulfilled the criteria set out in *The Diagnostic and Statistical Manual of Mental Disorders 5th edition* (American Psychiatric Association, 2013) for major depressive disorder, and mianserin (10 mg) was prescribed for his depression.

With regard to other findings, because his dietary intake had been decreased for more than two weeks and the storage of vitamin B1 in the body is known to be approximately 18 days (MacLean et al., 1983), thiamine deficiency was suspected and blood samples showed the concentration of vitamin B1 to have fallen to 20 ng/mL (reference range: 24–66 ng/mL).

The patient was treated with oral vitamin B1 administration (75 mg/day) and no onset of WE was observed. His depression was resolved after six months because of the continuation of drug therapy and psychotherapy, and no recurrence has been observed to date.

Discussion

We identified thiamine deficiency in the bereaved who had lost their spouses to cancer. Surviving family members present with various physical symptoms depending on the stress levels; however, to the best of our knowledge there have been no reports of thiamine deficiency to date. Thus, these case studies can be said to present new information for further consideration. The patients in these cases did not present with any of the classical symptoms of WE: disturbed consciousness, ataxia, and ocular symptoms. Previous studies have shown that these symptoms show low sensitivity, and cases without any of the three symptoms have been reported (Isenberg-Grzeda et al., 2017; Onishi et al., 2018d).

The key to the diagnosis of thiamine deficiency was the decrease in appetite lasting more than two weeks. Thiamine deficiency can occur any time nutrition is unbalanced for a period of two to three weeks (Sechi et al., 2016b) because thiamine is only stored in the body for about 18 days (MacLean et al., 1983).

A reduction in dietary intake is regarded as the major cause of WE onset, although malabsorption of thiamine resulting from old age may also be involved (Chen et al., 1996; Nichols & Basu, 1994; Vir & Love, 1977).

In case 2, we administered thiamine orally. Intravenous thiamine administration of >200 mg/day is recommended for the treatment of WE (Galvin et al., 2010; Isenberg-Grzeda et al., 2012). In elderly patients, oral thiamine (10 mg/day) was reported to improve the quality of life compared with a placebo (Wilkinson et al., 1997). We think that the ability to absorb thiamine via the small intestine remained intact in this case.

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In case 2, symptoms of depression appeared foremost, with no symptoms indicative of thiamine deficiency, other than decreased appetite, observed. Because the death of a spouse is the greatest risk factor for the development of depression in the elderly (Cole & Dendukuri, 2003), it is important to keep depression in mind during medical treatment. However, physical symptoms other than depression, such as those observed in the present case, should also be noted.

In conclusion, although the diagnosis and treatment of mental illness as well as the provision of grief care are important for survivor care, it is also vital to pay close attention to physical problems such as thiamine deficiency.

References

American Psychiatric Association (2013) *Diagnostic and statistical manual of mental disorders*, 5th ed, Washington DC: American Psychiatric Publishing.

Carey IM, Shah SM, DeWilde S, *et al.* (2014) Increased risk of acute cardiovascular events after partner bereavement: A matched cohort study. *JAMA Internal Medicine* **174**(4), 598–605.

Chen MF, Chen LT, Gold M, *et al.* (1996) Plasma and erythrocyte thiamin concentrations in geriatric outpatients. *Journal of the American College of Nutrition* **15**(3), 231–236.

Cole MG and Dendukuri N (2003) Risk factors for depression among elderly community subjects: A systematic review and meta-analysis. *American Journal Psychiatry* **160**(6), 1147–1156.

Erlangsen A, Jeune B, Bille-Brahe U, *et al.* (2004) Loss of partner and suicide risks among oldest old: A population-based register study. *Age and Ageing* **33**(4), 378–383.

Galvin R, Brathen G, Ivashynka A, *et al.* (2010) EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. *European Journal of Neurology* **17**(12), 1408–1418.

Holmes TH and Rahe RH (1967) The social readjustment rating scale. *Journal of Psychosometric Research* **11**(2), 213–218.

Isenberg-Grzeda E, Alici Y, Hatzoglou V, *et al.* (2016a) Nonalcoholic thiamine-related encephalopathy (Wernicke-Korsakoff syndrome) among inpatients with cancer: A series of 18 cases. *Psychosomatics* **57**(1), 71–81.

Isenberg-Grzeda E, Hsu AJ, Hatzoglou V, *et al.* (2015) Palliative treatment of thiamine-related encephalopathy (Wernicke's encephalopathy) in cancer: A case series and review of the literature. *Palliative and Supportive Care* **13** (5):1241–1249.

Isenberg-Grzeda E, Kutner HE, and Nicolson SE (2012) Wernicke-Korsakoff-syndrome: Under-recognized and under-treated. *Psychosomatics* **53**(6), 507–516.

Isenberg-Grzeda E, Rahane S, DeRosa AP, *et al.* (2016b) Wernicke-Korsakoff syndrome in patients with cancer: A systematic review. *Lancet Oncology* **17**(4), e142–e148.

Isenberg-Grzeda E, Shen MJ, Alici Y, *et al.* (2017) High rate of thiamine deficiency among inpatients with cancer referred for psychiatric consultation: Results of a single site prevalence study. *Psychooncology* **26**(9), 1384–1389.

Ishida M, Onishi H, Wada M, *et al.* (2010) Bereavement dream? Successful antidepressant treatment for bereavement-related distressing dreams in patients with major depression. *Palliative and Supportive Care* **8**(1), 95–98.

Ishida M, Onishi H, Wada M, *et al.* (2011) Psychiatric disorders in patients who lost family members to cancer and asked for medical help: descriptive analysis of outpatient services for bereaved families at Japanese cancer center hospital. *Japanese Journal of Clinical Oncology* **41**(3), 380–385.

Ishida M, Onishi H, Wada M, *et al.* (2012) Psychological distress of the bereaved seeking medical counseling at a cancer center. *Japanese Journal of Clinical Oncology* **42**(6), 506–512.

Ishida M, Onishi H, Toyama H, *et al.* (2015) Missing memories of death: Dissociative amnesia in the bereaved the day after a cancer death. *Palliative and Supportive Care* **13**(6), 1787–1790.

Ishida M, Onishi H, Morita T, *et al.* (2018) Communication disparity between the bereaved and others: What hurts them and what is unhelpful? A nationwide study of the cancer bereaved. *Journal of Pain and Symptom Management* **55**(4), 1061–1067.e1061.

Kaprio J, Koskenvuo M, and Rita H (1987) Mortality after bereavement: A prospective study of 95,647 widowed persons. *American Journal of Public Health* **77**(3), 283–287.

Li G (1995) The interaction effect of bereavement and sex on the risk of suicide in the elderly: An historical cohort study. *Social Science & Medicine* **40**(6), 825–828.

MacLean LD, Rhode BM, and Shizgal HM (1983) Nutrition following gastric operations for morbid obesity. *Annals of Surgury* **198**(3), 347–355.

Nichols HK and Basu TK (1994) Thiamin status of the elderly: Dietary intake and thiamin pyrophosphate response. *Journal of the American College of Nutrition* **13**(1), 57–61.

Onishi H, Ishida M, Kagamu H, *et al.* (2018a) Wernicke encephalopathy in a lung cancer patient during treatment with nivolumab. *Palliative and Supportive Care* 1–3.

Onishi H, Ishida M, Takahashi T, *et al.* (2018b) Wernicke encephalopathy without delirium that appeared as agitation in a patient with lung cancer. *Palliative and Supportive Care* **16**(6):800–802.

Onishi H, Ishida M, Tanahashi I, *et al.* (2018c) Early detection and successful treatment of Wernicke's encephalopathy in outpatients without the complete classic triad of symptoms who attended a psycho-oncology clinic. *Palliative and Supportive Care* **16**(5), 633–636.

Onishi H, Ishida M, Tanahashi I, *et al.* (2018d). Subclinical thiamine deficiency in patients with abdominal cancer. *Palliative and Supportive Care* **16**(4), 497–499.

Onishi H, Ishida M, Tanahashi I, *et al.* (2018e) Wernicke encephalopathy without delirium in patients with cancer. *Palliative and Supportive Care* **16**(1), 118–121.

Onishi H, Ishida M, Toyama H, *et al.* (2016) Early detection and successful treatment of Wernicke encephalopathy in a patient with advanced carcinoma of the external genitalia during chemotherapy. *Palliative and Supportive Care* **14**(3), 302–306.

Onishi H, Ishida M, Uchida N, *et al.* (2018f) Subclinical thiamine deficiency identified by preoperative evaluation in an ovarian cancer patient: Diagnosis and the need for preoperative thiamine measurement. *Palliative and Supportive Care* 1–2.

Onishi H, Ishida M, Uchida N, *et al.* (2019) Thiamine deficiency observed in a cancer patient's caregiver. *Palliative and Supportive Care* 1–3.

Sechi G, Batzu L, Agro L, *et al.* (2016a) Cancer-related Wernicke-Korsakoff syndrome. *Lancet Oncology* **17**(6), e221–e222.

Sechi G, Sechi E, Fois C, *et al.* (2016b) Advances in clinical determinants and neurological manifestations of B vitamin deficiency in adults. *Nutrition Reviews* **74**(5), 281–300.

Victor M, Adams RD, and Collins GH (1971) The Wernicke-Korsakoff syndrome. A clinical and pathological study of 245 patients, 82 with post-mortem examinations. *Contemporary Neurology Series* **7**, 1–206.

Vir SC and Love AH (1977) Thiamine status of institutionalised and non-institutionalised aged. *International Journal for Vitamin and Nutrition Research* **47**(4), 325–335.

Wilkinson TJ, Hanger HC, Elmslie J, *et al.* (1997) The response to treatment of subclinical thiamine deficiency in the elderly. *American Journal of Clinical Nutrition* **66**(4), 925–928.

Zisook S and Shuchter SR (1991) Depression through the first year after the death of a spouse. *American Journal Psychiatry* **148**(10), 1346–1352.

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