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Thiamine deficiency in the outpatient psychiatric oncology setting: A case series

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Case Report

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Abstract

Objective. B vitamins are essential for the functioning of the nervous system. Vitamin B1 (thiamine) deficiency is associated with neuropsychiatric syndromes such as Wernicke's encephalopathy (WE), which, if untreated, has an estimated mortality of 17–20%. Although the prevalence of thiamine deficiency in the general population is difficult to estimate, it is being increasingly recognized in oncology, especially in the inpatient setting. We describe three cases of thiamine deficiency (TD) in the outpatient psychiatric oncology setting.

Method. Retrospective chart review of three adult patients, who were seen in the psychiatric oncology clinic and found to have TD on laboratory testing, was done. Patient, disease, and thiamine treatment-related information were obtained, and descriptive statistics were used to analyze the data.

Results. The average age was 59 years, mean body mass index (BMI) was 22.00 ± 4.58 (mean ± SD), and mean thiamine level was 59.10 ± 7.69 that ranged from 45 to 68 nmol/L (normal thiamine level reference: 70–180 nmol/L). None of the patients had brain imaging nor cerebrospinal fluid analysis. Risk factors such as unbalanced nutrition, prior GI surgery, renal disease, and chemotherapy were noted.

Significance of results. TD can have a multifactorial etiology in oncology. Identification of TD in both inpatient and outpatient setting is important. Our report highlights how early identification of TD in the outpatient setting can help prevent further clinical progression.

Introduction

Thiamine (vitamin B1) is an essential vitamin required for nervous system function (Thomson and Marshall, 2006). Thiamine deficiency (TD) is associated with Wernicke's encephalopathy (WE), an acute neuropsychiatric condition that can present as confusion, ataxia, and ophthalmoplegia (Thomson and Marshall, 2006). Although often associated with alcoholism (Sanvisens et al., 2017), TD is also seen in other conditions linked to poor nutritional balance (Sechi and Serra, 2007), including cancer (Isenberg-Grzeda et al., 2016b). Using thiamine level to estimate the prevalence of TD, a study found 55.3% of hospitalized cancer patients to have TD (Isenberg-Grzeda et al., 2017). Cancer patients are vulnerable to TD due to increased demand by tumor cells, reduced oral intake, lack of absorption, and altered thiamine metabolism from drug interactions with chemotherapeutic agents. (Pirzada et al., 2000; Kwon et al., 2010; Isenberg-Grzeda et al., 2016b). Additionally, cancer and cancer treatment can confound cognitive symptoms, highlighting the importance of TD identification in oncology (Pelgrims et al., 2000; Cefalo et al., 2014).

Diagnosis of TD can be challenging. Only 16% of patients present with the classic triad (Harper et al., 1986), leading to the proposal of new diagnostic criteria for WE (Caine et al., 1997). Diagnostic tools include blood thiamine levels and brain MRI (Boros et al., 1998; Isenberg-Grzeda et al., 2016b). Brain imaging findings can vary widely (Zuccoli et al., 2009) and the sensitivity is only 53% (Antunez et al., 1998). As such, WE remains a clinical diagnosis that requires a high index of suspicion (Isenberg-Grzeda et al., 2016b). Even after TD is diagnosed, treatment is complicated by the lack of standardized guidelines with regards to formulation, dose, and duration of thiamine supplementation (Day et al., 2013). Although parenteral administration is encouraged (Thomson et al., 2002; Galvin et al., 2010), researchers noted only 29% of thiamine orders were via the intravenous route (Nakamura et al., 2018).

Given these difficulties in diagnosis and treatment, one area worthy of study is prevention. Because TD is the cause of WE, early recognition of TD can potentially decrease the incidence of WE. TD has mostly been described in the inpatient oncology setting (Isenberg-Grzeda et al., 2016a) thus far in the United States. However, TD has been noted in the outpatient setting in Japan (Onishi et al., 2018c) and with delayed symptom onset post-discharge (Restivo et al., 2016). We describe three cases of TD in the outpatient oncology setting, with a focus on identifying features that may improve detection of TD.

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Table 1. Demographics

Case	Age	BMI	Reason for consult	Cancer	Cancer stage	XRT completed (days)	Therapy (chemo or hormone or immune or phase I)	Surgery
1	73	27	"Recent loss of daughter, with signs of depression, weight loss, low appetite."	Multiple myeloma	II	96	CyBorD (Cyclophosphamide, Bortezomib, Dexamethasone)	No
2	56	21	"With recurrent breast cancer and long-standing anxiety, disorganized thoughts, lack of attention, depression."	Relapse of breast cancer	IV	112	Letrozole, Palbociclib	No
3	46	18	"Patient having anxiety and depression."	Pancreas	IV	NA	FOLFIRINOX (Leucovorin, 5-FU, Irinotecan, Oxaliplatin)	Yes — GI surgery 531 days prior to the psychiatry consult

BMI, Body Mass Index; XRT, radiation; GI, gastrointestinal; 5FU, Fluorouracil.

Table 2. Medical Comorbidities — Unbalanced Nutrition (which were noted within 7 days of the psychiatric evaluation)

Case	Weight loss	Nausea	Diarrhea	Prolonged fasting	Psychogenic food refusal	Alzheimer's disease	FTT	TPN use
1	Yes	Yes	No	No	No	No	No	No
2	No	No	No	No	No	No	No	No
3	Yes	No	No	No	No	No	No	No

Table 3. Medical Comorbidities — Risk factors associated with metabolism or excretion

Case	Thyrotoxicosis	Renal disease	Chronic infectious disease	Crohn's disease	Other medical condition (Top 2 diagnoses mentioned after cancer diagnosis in the oncology note at the time)
1	No	Yes	No	No	Yes — Folate deficiency and vitamin D deficiency, chronic kidney disease (GFR:39 mL/min/1.73 m^2)
2	No	No	No	No	Yes — Tobacco use
3	No	No	No	No	Yes — Abdominal ascites, Horner's Syndrome

Methods

One of the authors reviewed the medical charts of three adult patients seen for outpatient psychiatric clinic. Thiamine blood levels were used to identify patients with TD. Because of the descriptive nature of the report, there were no exclusion criteria. Information regarding (a) demographics, (b) medical comorbidities, (c) laboratory results, (d) mental status exam, (e) neurological exam, and (f) thiamine-related treatment were obtained from the chart.

The institution review board approved the study and informed consent was waived.

Data analysis

Descriptive statistics was used for the data analysis: continuous data expressed in mean and standard deviation, categorical data expressed in percentage.

Results

Demographics

Patients with TD were 73, 56, and 46 years old (Tables 1–3). Two patients had solid organ tumors and the third had multiple myeloma. At the time of evaluation, all patients were in some form of cancer treatment. For all three patients, the reason for psychiatric referral was depression and one had an additional cognitive concern. None of the patients reported recent alcohol use.

The most common medical comorbidity was weight loss, followed by nausea and renal disease. However, all patients maintained nutrition orally. Only one patient was seen by neurology within 20 days of the psychiatric evaluation.

Neurological examination

One of the three patients had some difficulty with orientation questions, but not concentration (Table 6). One felt too weak to walk, and so was in a wheelchair. The remaining two patients ambulated independently. None of the patients had ocular, cerebellar, nor involuntary movements.

Laboratory results

Blood thiamine was 68, 54, and 45 nmol/L, respectively (Tables 4 and 5). One patient had chronic kidney disease of moderate to severe degree, but the rest of the results were normal. None of them had brain imaging nor cerebrospinal fluid analysis within

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Table 4. Laboratory results

Case	WBC (4.0–11.0 K/μL)	Platelet (140–440 K/μL)	Cr (0.67–1.17 mg/dL)	Na (136–145 mEq/L)	K (3.6–5.1 mEq/L)	TSH/FT4 (0.27–4.20 mcunit/mL/0.93–1.70 ng/dL)	Mg (1.6–2.6 mg/dL)	B1 (70–180 nmol/L)	B12 (211–946 pg/mL)
1	4.5	107	1.51	141	4.4	2.49/–	1.9	68	6849
2	2.6	185	0.86	142	4.7	2.68/1.82	–	54	278
3	6.3	399	0.58	132	4.3	–	2.0	45	2454

WBC, White Blood Count; Cr, Creatinine; Na, Sodium; K, Potassium; Mg, Magnesium; TSH, Thyroid Stimulating Hormone; FT4, Thyroxine Free Level; B1, Whole Blood Thiamine Level. B6 — none of the patients had B6 levels at the time of evaluation.

Table 5. Laboratory results continued

Case	ALT/AST (<33 U/L/ <32 μ/L)	Alk PO4 (35–104 U/L)	Total Bilirubin (<1.2 mg/dL)	Direct Bilirubin (<0.3 mg/dL)	Albumin (3.5–5.2mg/dL)
1	11/14	88.0	1.0	–	3.80
2	8.0/18.0	74.0	0.30	–	4.80
3	25/31	413.0	0.30	–	0.00

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; Alk PO4, Alkaline Phosphatase.

10 days of the psychiatric evaluation. Albumin levels were normal and vitamin B12 levels were in the normal to high range.

Mental status and thiamine treatment

Of the three, two had concern for depressed mood and one had grief reaction (Table 6). Based on thiamine results, thiamine replacement was offered. One patient refused, one took oral thiamine, and one was given parental thiamine during the admission immediately after psychiatric evaluation. Refusal was due to the patient's health beliefs regarding vitamin usage in cancer.

Discussion

We describe the clinical characteristics of three patients with TD in the outpatient psychiatric oncology setting. Early identification of TD is important to prevent complications like WE. One patient displayed a possible manifestation of WE in the form of mild cognitive impairment. This highlights the importance of early identification of TD and the possibility of such, even in the outpatient setting.

The common theme for outpatient psychiatric consultation was depression. Depression is more common in cancer patients (Mitchell et al., 2011) with psychological symptoms more indicative of depression than neurovegetative symptoms (changes in appetite, sleep, and energy level (Dantzer et al., 2008)) of depression. It is important to distinguish between the two types of symptoms for appropriate management. Neurovegetative symptoms may shed light on the nutritional status, that would guide further tests such as thiamine level. In our report, in addition to psychological symptoms of depression, two patients had appetite loss with weight loss (one patient had a BMI of 18). Therefore, thiamine level was considered in all three. Thiamine levels can help identify those at risk for WE (Thomson et al., 2002), so that timely repletion can prevent progression to WE.

Decreased appetite, whether due to neurovegetative symptoms of depression, cancer progression, or cancer treatment, is a serious concern in cancer patients. Researchers have suspected TD even in the absence of cognitive changes, based on a history of appetite loss for more than 2 weeks (Onishi et al., 2018d, 2018e, 2019). In patients with poor nutritional status, the evaluation of other B vitamin levels may be natural. In our report, two of three patients had normal folate levels and all had normal or high vitamin B12 levels. High B12 levels were due to recent vitamin replacement and longer body stores (Nielsen et al., 2012). Interestingly, the majority of patients with TD in the inpatient oncology setting had normal B12 and folate (Isenberg-Grzeda et al., 2017). Our results highlight the importance of screening for TD in patients with poor oral intake, even in the absence of other vitamin level abnormalities.

Historically, WE was observed in certain types of cancer: greatest number reported in hematological cancers, followed by gastrointestinal (GI) cancers (Isenberg-Grzeda et al., 2016b). Possible reasons may be increased demand due to rapid cell turnover for hematological cancers, and decreased intake, absorption, and use of parental nutrition after surgical resection for GI cancers. This is reflected in our case series. Our third patient had advanced breast cancer. Although there are fewer reports of breast cancer presenting with TD (Aksoy et al., 1980; Kuo et al., 2009; Onishi et al., 2018e), this cancer should not be overlooked when screening for TD.

TD is common during or soon after chemotherapy, specifically with antimetabolite and alkylating agents (Boros et al., 1998). Of the various chemotherapeutic agents, 5-FU interferes with the formation of the biologically active form of thiamine (Pirzada et al., 2000) and reduces thiamine levels in the liver and spleen (Aksoy et al., 1980). The above effects were significant even when compared with other chemotherapeutic agents (Aksoy et al., 1980). This condition was recognized in one patient, who had received treatment with 5-FU.

Our report describes the clinical characteristics of TD in the outpatient oncology setting. To our knowledge, TD in the

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Table 6. Mental status and thiamine treatment

Case	Depression symptoms during psychiatric evaluation	Psychiatric mental status evaluation	Thiamine given after consultation	Thiamine route	Thiamine dose	Repeat thiamine level (nmol/L)
1	Psychological symptoms: Reported mood as "adjusting," with variable concentration, but denied guilt and denied suicidal ideation. Neurovegetative symptoms: Decreased appetite due to chemotherapy and decreased energy.	Difficulty with identification of the correct month, but after prompting was able to answer accurately. Oriented to place and self, with fair concentration. Gait: normal. Abnormal movements: none. Concern for grief reaction.	Yes	PO	>250 mg/d	91
2	Psychological symptoms: Reported mood as "angry", associated with worthlessness, easy irritability, but denied active suicidal ideation. Neurovegetative symptoms: Decreased appetite and decreased energy.	Tangential thought process that required frequent redirection, with intermittent loud speech. However, good concentration. Gait: normal. Abnormal movements: none. Concern for depressed mood.	Offered, but patient refused trial of thiamine replacement.	–	–	–
3.	Psychological symptoms: Reported mood as "fatigued", with some guilt related to role responsibility and sadness related to dependence on others. Generalized weakness, so was unable to ambulate. Denied suicidal ideation. Neurovegetative symptoms: Decreased appetite and significant weight loss, which resulted in dissatisfaction with physical appearance. Reported anxiety about disease status.	Oriented to time, place, person, and had intact concentration. Soft-spoken, with intermittent tearfulness talking about dependence on others, but denied suicidal ideation. Gait: in wheelchair. Abnormal movements: none. Concern for depressed mood and anxiety.	Yes	IV	>250 mg/d	No

outpatient oncology setting has been limited to case reports in Japan (Onishi et al., 2018a, 2018b, 2018e, 2019, 2020). Similar to Onishi et al., patients in our report have different types of cancer, but most were in the advanced stage with more determinants of unbalanced nutrition. Although their case reports utilized thiamine level, the results were not comparable to ours. Our report adds to the existing literature by capturing TD in cancer outpatients, possibly at an earlier stage, prior to the development of severe WE. As in other studies, we noted various possible causes of unbalanced nutrition. However, we also provide information about the presence or absence of medical conditions which may contribute to TD.

Our report has some limitations. Due to the retrospective design, data are limited to the visit documentation and details about degree of weight loss or duration of nausea were not obtained. Although two patients agreed to thiamine replacement, repeat thiamine level was only obtained in one patient. Because identification of TD in the outpatient setting was the goal, treatment-related factors were not explored in the current paper. However, this could be expanded in future studies. Lastly, a larger study could address the concern with the small sample size.

Conclusion

Cancer patients have numerous risk factors for TD and are at risk for WE. Thiamine levels can help identify patients at risk. Identification of at-risk patients who have not yet manifested symptoms of WE would allow for timely treatment. In the setting of poor oral intake as a neurovegetative symptom of depression in the outpatient psychiatric clinic, the most common clinical presentations were weight loss and orientation difficulty. It is hoped that early detection of TD in cancer patients may prevent sequelae and improve overall clinical outcome in this vulnerable population.

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