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Nonalcoholic Thiamine-Related Encephalopathy (Wernicke-Korsakoff Syndrome) Among Inpatients With Cancer: A Series of 18 Cases

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Background: *Wernicke-Korsakoff Syndrome (WKS) is a neuropsychiatric syndrome caused by thiamine deficiency. Cancer predisposes to thiamine deficiency through various mechanisms. Although many case reports exist on nonalcoholic WKS in cancer, larger qualitative studies are lacking.* **Method:** *Retrospective study of patients admitted to a cancer hospital and diagnosed with WKS during routine care on a psychiatric consultation service. Only patients with at least 1 additional supporting feature (magnetic resonance imaging findings, low serum thiamine concentrations, or response to treatment) were included. Data pertaining to demographics, risk factors, phenomenology, and outcomes were abstracted from medical records by chart review.* **Results:** *In all, 18 patients were included. All patients developed WKS during cancer treatment. Hematologic malignancy, gastrointestinal tract tumors, low oral intake, and weight loss were common risk factors. All patients presented with cognitive dysfunction, most commonly impaired alertness, attention, and short-term memory. All were diagnosed by operational criteria proposed by Caine et al., 1997 (where 2 of the following are required: nutritional deficiency, ocular signs, cerebellar signs, and either altered mental status or mild memory impairment). Few exhibited Wernicke's classic triad. Diagnostic and treatment delay were common. Only 3 patients recovered fully.* **Conclusion:** *Nonalcoholic WKS can occur during cancer treatment and manifests clinically as delirium. Diagnosis should be made using operational criteria, not Wernicke's triad. Most patients were not underweight and had normal serum concentration of vitamin B_{12} and folate. A variety of mechanisms might predispose to thiamine deficiency and WKS in cancer. Given the high frequency of residual morbidity, studies should focus on decreasing diagnostic and treatment delay.*

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INTRODUCTION

Background

Wernicke-Korsakoff Syndrome (WKS) is a neuropsychiatric syndrome associated with thiamine (vitamin B_1) deficiency (TD).[1] Thiamine is a cofactor for enzymes involved in energy production throughout the body including within muscle, hepatocytes, and

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neurons. Thiamine must be acquired from the diet, and owing to its high rate of turnover,[2] daily intake is needed to maintain homeostasis. In healthy individuals the body stores up to 2–3 weeks necessity of thiamine, thereby adding a small buffer against disruption in thiamine homeostasis. Such disruption occurs under conditions causing any combination of decreased thiamine availability, accelerated usage, impaired functioning, or excessive loss of thiamine.[3] Decreased availability occurs during starvation, malnutrition, malabsorption, and vomiting.[3] Accelerated thiamine usage occurs in hypermetabolic states, such as during alcohol withdrawal, seizures, infections, critical illness, with fast-growing tumors, diabetes, or following glucose or dextrose loading.[3] Impaired use of thiamine occurs through the direct inactivating effects of certain medications, including metronidazole and fluorouracil, which have been proposed as risk factors for nonalcoholic WKS.[4–7] Finally, excessive loss leading to TD has been reported in diabetes,[8] hemodialysis,[9] and with diuretic use.[10]

Pathophysiology

When TD is severe enough, cells lose their ability to produce aerobic energy and cause buildup of lactic acid and reactive oxygen species.[11] Within a matter of days, cell death begins. In the brain, this pathophysiologic process leads to characteristic neuroanatomic lesions in the medial thalami, mammillary bodies, tectal plate, periaqueductal area of the midbrain, and periventricular regions of the third ventricle, though atypical findings in the cerebral cortex, cerebellum, and cranial nerve nuclei have also been described.[12] When this disease process leads to an observable, clinical syndrome, it is referred to as the WKS. Although historically believed to be 2 separate entities, WKS is now considered to be a single syndrome with a single pathophysiologic mechanism and variable phenomenology.[13] Genetic variations of thiamine transporters have been proposed as an explanation for why TD leads to full-blown WKS in some individuals and not others.[14]

Clinical Factors

Clinically, WKS manifests with 1 or several cognitive, cerebellar, or ocular findings, thus making it relevant to both neurology and psychiatry consultants. The prevalence is up to 2% among the general population[15] and up to 12.5% among patients with alcohol use disorders.[16] The notion of Wernicke's classic triad (confusion, ataxia, and nystagmus) as a reliable diagnostic tool has been refuted[3] as it is present in only 16% of cases.[17] By using the operational criteria proposed by Caine et al.,[18] diagnostic sensitivity increases to 85%, and a diagnosis can be made when patients have any 2 of the following 4 features: nutritional deficiency; ocular signs; cerebellar signs; either altered mental status or mild memory impairment. MRI is costly and lacks sufficient sensitivity to be a reliable diagnostic tool.[19] Still, MRI can confirm suspected WKS owing to its high specificity, and it can rule out other intracranial pathology. Serum thiamine concentration can identify TD and point toward an overall nutritional deficiency but cannot be used alone to diagnose WKS, which is a clinical syndrome. In addition, the laboratory test is not readily available in most hospitals.[20] Treatment consists of high-dose parenteral thiamine supplementation, which is safe, cheap, and effective when initiated early.[21] Unfortunately, WKS is often under-recognized, and up to 80% of cases are missed.[22] When not treated early and adequately, the downstream effects can include long-term and irreversible cognitive dysfunction, high costs of morbidity, and death.[23]

WKS in Cancer

Owing to historic factors, WKS has been studied mostly in patients with alcohol use disorders. This is changing, however, and an increasingly large body of literature is being published on nonalcoholic WKS among medical and surgical patient populations.[13] Cancer predisposes to TD through the same pathophysiologic mechanisms described earlier (decreased availability, accelerated usage, impaired functioning, and excessive losses). Higher rates of TD among patients with cancer have been reported in several small studies.[5,24] WKS has also been reported in cancer. The prevalence of WKS in patients who died following bone marrow transplants has been estimated in 2 studies, with estimates ranging from 6–33%.[25,26] The remainder of the literature on nonalcoholic WKS in cancer consists of case reports and small case series.[27,28]

The aim of this study is to report on 18 cases of nonalcoholic WKS in patients with cancer who were admitted to an acute care cancer hospital. Our goal was to address the gaps in the literature by describing