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Review Article

Wernicke-Korsakoff syndrome despite no alcohol abuse: A summary of systematic reports

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ABSTRACT

Background: Wernicke-Korsakoff syndrome (WKS) is a neurological disorder typically found in alcohol use disorder. The fact that it also occurs in nonalcoholic patients is less well known and often ignored. For the first time, this review offers a systematic investigation of the frequency and associated features of nonalcoholic WKS in the published literature.

Method: We included 11 recent systematic reports, with a total of 586 nonalcoholic WKS cases following hyperemesis gravidarum ($n = 177$), cancer ($n = 129$), bariatric surgery ($n = 118$), hunger strike ($n = 41$), soft drink diet in children ($n = 33$), depression ($n = 21$), Crohn's disease (n = 21), schizophrenia ($n = 15$), anorexia nervosa ($n = 12$), ulcerative colitis ($n = 10$), and incidental thiamine-deficient infant formula ($n = 9$).

Findings: Vomiting and extreme weight loss were strong predictors of nonalcoholic WKS in adults. Blurred vision was a common presenting sign in about one-fourth of the patients. The classic triad of WKS is characterized by confusion, ataxia, and eye-movement disorders. All reviewed studies reported high percentages of patients presenting with an altered mental status, while both motor symptoms were variably present.

Interpretation: The foregoing observations led to several important conclusions. First, we can see that nutritional impoverishment leads to profound brain damage in the form of WKS. Second, it seems that physicians are either unaware of or underestimate the risks for nonalcoholic WKS. Physicians must be specifically vigilant in detecting and treating WKS in patients with sudden and severe weight loss and vomiting. Third, lower doses of thiamine frequently lead to chronic Wernicke-Korsakoff syndrome. We noticed that when thiamine treatment for WKS was administered, in many cases doses were too low. In line with proven interventions we therefore recommend a parenteral thiamine treatment of 500 mg 3 times per day in adults.

1. Introduction

Wernicke-Korsakoff syndrome (WKS) is a neurological disorder caused by thiamine (vitamin B1) deficiency. Wernicke Encephalopathy (WE), the acute phase of this syndrome, was characterized by Carl Wernicke in 1881, as a triad of altered mental status, ocular signs, and ataxia. The chronic phase of WKS, called Korsakoff's syndrome (KS), was described by Sergei Korsakoff in 1887, as an amnesic disorder with confabulations [1–4]. WKS most typically develops after malnourishment in chronic self-neglecting patients with an alcohol use disorder (AUD). Thiamine deficiency is common in AUD because alcohol is high in calories but poor in nutrients. Also, diarrhea and liver problems in AUD leads to improper storage of thiamine. Moreover, due to self-neglect and alcohol consumption, patients have impaired enzymatic and bacterial functioning, and are therefore at risk for nutritional deficiency, including magnesium [3,4].

Of interest, alcohol is not a necessary contributing factor to WKS. In Carl Wernicke's first WE report, a nonalcoholic 20-yearold woman developed pyloric stenosis, a narrowing of the stomach opening, after sulphuric acid ingestion. She continued vomiting and developed WE. Also, in addition to Sergei Korsakoff's description of his eponymous amnesic disorder in “more than 30” AUD cases, he also described eight cases following prolonged vomiting unrelated to alcohol consumption, and eight other cases with chronic infections, post-partum illness, and vomiting after poisoning [5]. Notably, in most of these patients a comorbid neuropathy was also documented [6]. The variety of case descriptions by Wernicke and Korsakoff suggested a diverse etiology of WKS. Despite their extensive description of WE and KS, they had failed

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to recognize the underlying primary cause: a nutritional deficiency. It took five more decades before the direct contribution of vitamin deficiency was well-established. Captain De Wardener and Lennox described the prospective relationship between a lack of vitamin B1 following malnourishment and WKS in prisoners of war in Singapore [2].

In modern medicine, patients who have a severely diminished intake or practice fasting for a prolonged time, can resemble the patients described by DeWardener and Lennox in their development of WKS. Famine, which often leads to the consumption of a diet with only polished rice, hunger strikes, food refusal in anorexia nervosa, depression and schizophrenia, are some of the examples that can lead to WKS [4,5,13–17]. Less familiar is the risk of giving total parenteral nutrition without thiamine to already weakened individuals, or accidentally giving babies and children a diet without thiamine [14,16,19]. A second group of persons at risk of WKS are patients that vomit or have chronic diarrhea. Pregnant women that develop hyperemesis gravidarum, persons having complications after bariatric surgery, and inflammatory bowel disease have been described as causes of WKS [4,10,12,16]. A third group at risk for developing WKS, that have a higher need for thiamine and magnesium, are patients with cancer, Crohn's disease, and chronic diuretic therapy [4,5].

Over the years following the descriptions of DeWardener and Lennox, the reported cases that developed WE and KS following AUD outnumbered the nonalcoholic cases. Victor, Adams and Collins described a series of 245 patients, linking the acute WE and chronic KS as different phases of WKS only in AUD patients [7]. In response to the reports on alcoholic WKS, Freund (1976) even argued against the existence of nonalcoholic KS claiming there was no unequivocal proof of nutritional depletion causing KS [8]. The consequence of this claim has been that for years KS was viewed as the unavoidable outcome of structural alcohol use. As a result, the nutritional risks have been largely ignored. Fortunately, this mistake seems to have been corrected in the recent past. The number of reports on nonalcoholic WKS has risen exponentially. In fact, more than half of the published nonalcoholic WKS studies in hyperemesis gravidarum and obesity surgery were published in the last decade, suggesting a renewed interest in nonalcoholic WKS.

Because WKS is under-recognized and undertreated among patients without AUD, and because of the fast-rising number of both case reports and reviews on nonalcoholic WKS [3,10–19], we have brought together for the first time a complete overview of the systematic reports on nonalcoholic WKS. Our primary goal was to increase the clinician's awareness and recognition for nonalcoholic WKS by describing symptomatology, method of diagnosis, and outcome of treatment. Also, by increasing awareness for WKS in nonalcoholic patients, our second aim was to minimize the catastrophic consequences of not treating WKS adequately.

2. Methods

2.1. Study design

No research protocol has been registered, and there was no funding for this project. We performed a systematic review of the literature. We included systematic reviews reporting on WKS in nonalcoholic patients. We excluded case studies, or when data on clinical presentation (such as the symptomatology) were not reported.

2.2. Wernicke Encephalopathy and nonalcoholic cause

Reports were considered for inclusion if at least one of the following methods of diagnosing WE was reported and the findings reported in the case description were consistent with the classical triad of WE [5]: Ataxia, Eye-Movement Disorders (reported as nystagmus or opthalmoplegia), and Mental Status Change (reported as delirium, confusion, and problems in alertness, or cognition). Furthermore, all systematic reports had to cover a nonalcoholic cause of WKS. All reviews including alcoholic patients were therefore not included.

2.3. Search strategy and study selection

The MEDLINE online database was searched, via the PubMed interface, using the search term "Wernicke Encephalopathy"[Mesh] OR "Korsakoff Syndrome"[Mesh] OR "Thiamine Deficiency"[Mesh] AND systematic. The search was limited to humans, English language, and publication date from 2000 onwards. All retrieved articles were manually screened for original systematic reviews of nonalcoholic Wernicke's encephalopathy. In case multiple studies reported on the same cause of WKS, the most recent study was included. The MEDLINE search, which was last searched on 31 March 2021 retrieved 163 articles (see Fig. 1). Titles and abstracts were screened. The first author was involved in the selection process, as the selection criteria were straightforward.

2.4. Outcomes

We extracted and indexed the following data: diagnosis prior to WKS, number of reported cases, age, weight, etiology and onset, ataxia, eye-movement disorders, mental status change, MRI sensitivity, treatment, residual cognitive deficiencies/Korsakoff syndrome).

2.5. Treatment

According to the European Federation of Neurological Societies and the Royal College of Physicians, 500 mg of parenteral thiamine should be given 3 times daily until symptoms of acute WE resolve. The treatment is lifesaving and has the potential to reverse this acute neuropsychiatric syndrome [5]. Suboptimal treatment of WE is defined as <500 mg of parenteral thiamine as the initial dose to treat WE [5].

2.6. Statistical analysis

We analyzed the data with SPSS (version 25.0). We calculated descriptive statistics (medians, ranges, SD, frequencies, and

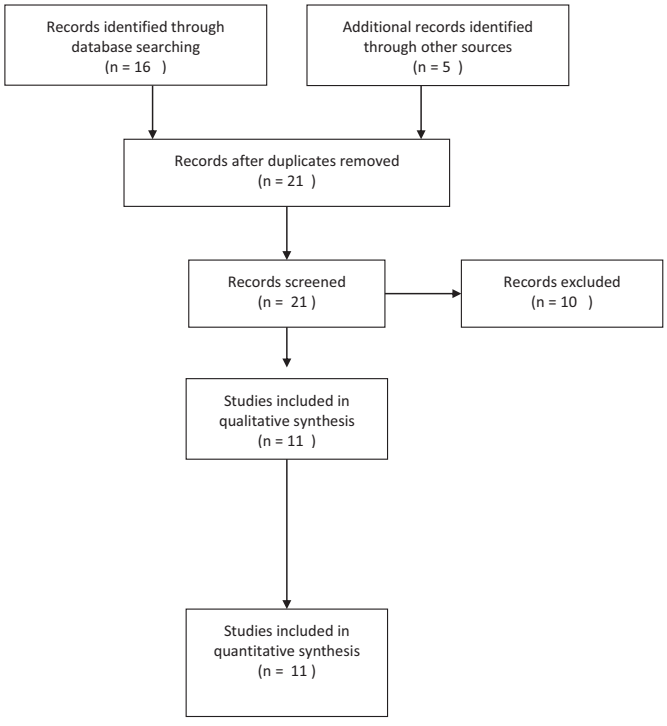

Fig. 1. Flow chart for the systematic review.

percentages) for article and patient demographics, symptoms, clinical features of WE, treatment dosing, and cognitive outcome. We calculated chi-square statistics for the three largest included nonalcoholic groups for the main symptoms of WKS, because these groups had a substantial number of participants for statistical analysis.

3. Results

3.1. General characteristics of nonalcoholic WKS patients

Patients diagnosed with WKS in nonalcoholic populations are relatively young. The average age for the 586 reviewed cases is 32.3 years (SD also: 32.3 years). We reviewed all studies in Table 1 of this manuscript. Nonalcoholic WKS is not restricted to an adult population. Pediatric WKS was evident in the studies on soft drink diet [14], and the study on accidental thiamine deficient infant formula [19]. In the study on Crohn's disease, a 5-year-old patient was included [16]. In the study on patients diagnosed with Anorexia Nervosa, one 13, one 14, one 15, and one 16-year-old patient were included [18]. Also, in the study on bariatric patients, one 14, two 15, and three 17-year-old patients were included [12].

Of interest, nonalcoholic WKS was more frequently observed in female patients than male patients. Hyperemesis gravidarum (100%) [10], but also in bariatric surgery (69.9%) [12], anorexia nervosa (10/12) [18], and cancer (55%) [19] female patients directly outnumbered the male patients. In all other conditions, the contribution of females to the review was also robust.

3.2. Warning signs of nonalcoholic WKS

3.2.1. Vomiting

In the most frequently described nonalcoholic WKS, namely hyperemesis gravidarum ($n = 177$) [10] and bariatric surgery ($n = 118$) [12], almost all patients had severe vomiting before the onset of WE. Patients with hyperemesis gravidarum had been vomiting for an average of 7 weeks before the onset of WE [10]. In obesity surgery, vomiting caused 87.3% of the cases [12]. Also, in other conditions, vomiting was a relatively common factor leading to a loss of vitamins. In babies and children on a soft drink diet [14], vomiting was evident in 22/33 cases. In 6/21 patients with depression [15], 8/21 patients with Crohn's disease [16], 2/15 schizophrenia patients [17], 5/10 ulcerative colitis patients [16], and 8/9 accidental thiamine deficient infant formula cases [18], vomiting was evident.

3.2.2. Massive weight loss

A second, but quite profound characteristic of nonalcoholic WKS patients seems to be massive weight loss prior to the development of WKS. As can be viewed in Table 1, the average weight loss ranged between at least 12 kg in hyperemesis gravidarum and 40 kg in hunger strike [10,13].

3.3. Presentation of nonalcoholic WKS

The clinical presentation of WKS is a triad of altered mental status, ocular signs, and ataxia which was present in all cases of hunger strike. In other populations, the full triad was present in at least half the patients for hyperemesis gravidarum (62.1%) [10], bariatric surgery (52.4%) [12], schizophrenia (12/15) [17], and anorexia nervosa 8/12 [18]. For the three largest samples, the classical triad was more frequently present in WKS following hyperemesis gravidarum compared to cancer ($\chi^2 = 31.92$, $p < .00001$). Also, in bariatric surgery the triad was more often present compared to cancer ($\chi^2 = 13.08$, $p < .001$). Following hyperemesis gravidarum and obesity surgery, a full classic triad was present in a comparable number of cases ($\chi^2 = 3.17, p = .074$).

3.3.1. Mental status change

All reviewed studies reported high percentages of patients presenting with an altered mental status, presenting as delirium, confusion, problems in alertness, and altered cognition. In all patients with hunger strike, mental status change was eventually present. Also, in the three largest groups, mental status change was a prominent characteristic of WKS: in 90% of the obesity surgery patients [12], 90% of the cancer patients [11], and 83.6% of the hyperemesis gravidarum patients [10]. This characteristic was not statistically the most pronounced in any of the three largest samples (ps > 0.11). In pediatric patients, an altered mental status was sometimes reflected by altered consciousness, irritability, and lethargy, as described in the study on soft drink diet in children [13] and in the accidental thiamine deficient infant formula report [17].

3.3.2. Ataxia

The two most described forms of ataxia were uncoordinated gait and truncal ataxia [10,12,13]. The reports on ataxia are variable, with 100% of the hunger strike patients [13], 84.7% of the bariatric surgery patients [12], and 83.1% of the hyperemesis gravidarum [10] patients with WKS presenting themselves with ataxia. In ulcerative colitis patients 50% had ataxia, and in cancer this sign was present in 52% [11]. For the three largest samples, ataxia was more frequently present in WKS following hyperemesis gravidarum compared to cancer ($\chi^2 = 34.35$, $p < .00001$). Also, in bariatric surgery ataxia was more present compared to cancer ($\chi^2 = 30.29$, $p < .00001$). Following hyperemesis gravidarum and obesity surgery, ataxia was present in a comparable number of cases ($\chi^2 = 0.15$, $p = .70$).

3.3.3. Eye-movement disorders

In depression, only 8/21 patients [15], and only 51% of the cancer patients [9] had eye-movement disorders as a sign of WKS. In the other two largest studies, eye-movement disorders were a prominent characteristic, with 86.4% of the hyperemesis gravidarum patients [10], and 73.7% of the bariatric patients [12] presenting themselves with eye-movement disorders. There were two additional relevant findings regarding eye-movement disorders: in obesity surgery there was an inverse relationship between body weight and a presentation with eye-movement disorders [12], suggesting that a higher body weight could protect against eye-movement disorders. Moreover, in anorexia nervosa patients [13], often both horizontal and vertical eye-movement disorders were present, possibly reflecting a more serious subtype of eye-movement disorders caused by full depletion of thiamine. For the three largest samples, eye-movement disorders were more frequently present in WKS following hyperemesis gravidarum compared to cancer ($\chi^2 = 43.88$, $p < .00001$). Also, in bariatric surgery eye-movement disorders were more present compared to cancer ($\chi^2 = 13.31$, $p < .001$). Following hyperemesis gravidarum eye-movement disorders were more often present compared to bariatric surgery ($\chi^2 = 6.73$, $p < .01$).

3.3.4. Vision

Visual disturbances were a common presenting sign of WKS. Blurred vision, including oscillopsia, or absence of vision is frequently reported in hyperemesis gravidarum (24%) [11], cancer (9%) [12], and ulcerative colitis (3/10) [17].

3.4. MRI findings

In line with the foregoing, concurrent brain scan data are specifically relevant. In 311 of the 586 cases MRI recording were available. In nonalcoholic WKS studies, MRI showed atrophy in the thalamic area, the mammillary bodies or the periaquaductal gray matter suggesting WKS in more than 66% of the cases, with a maximum sensitivity of 100% in schizophrenia and ulcerative colitis, 91% in hyperemesis gravidarum, and up to 79% sensitivity in cancer. In both pediatric studies, the sensitivity was between 50 and 60%.

Table 1
Diagnosis, number of cases, age, weight loss, primary etiology, symptomatology, treatment and outcome of non-alcoholic Wernicke-Korsakoff.

Diagnosis	Number of cases	Average Age in years (SD)	Average Weight loss in kg (SD)	Primary etiology and onset	Ataxia (% for n > 100, fraction for n ⟨100)	Eye-movement disorder (% for $n > 100$, fraction for $n < 100$)	Mental status change (% for n > 100, fraction for n < 100)	Full Triad (% for n > 100, fraction for n < 100)	MRI Sensitivity (% for n > 100, fraction for n < 100)	Low doses of thiamine treatment (<500 mg/day IV/IM), (% for n > 100, fraction for n < 100)	Residual cognitive deficits/ Korsakoff (% for n > 100, fraction for n < 100)
Hyperemesis Gravidarum	177	26.9 (5.5)	12.1 kg (5.9)	Vomiting for an average of 7 weeks. 33% presented with double vision, 24% with blurred vision	83%	86%	84%	62%	91%	64%	65%
Cancer	129	44 (22)	N.A.	Haematology cancer in 40%, Gastrointestinal in 36%	52%	51%	90%	29.5%	79%	43% <100 mg 44% > 200 mg	64%
Bariatric Surgery	118	36 (12.7)	N.A.	Vomiting in 87.3%	85%	74%	76%	52%	66%	77%	29%
Hunger strike	41	27.2 (2.5)	40.3	Fasting for a mean of 199 days (130–324 days)	41/41	41/41	41/41	41/41	N.A.	oral thiamine treatment in 100%	41/41
Soft drink diet in babies and children	33	1.3	N.A.	22 had vomiting, 11 had infections, 7 diarrhea. 20 presented with lethargy, 15 with edema	5/33	10/33	21/33	4/33	15/25	N.A.	9/27
Depression	21	47.2 (16.7)	14.9 (10.5)	7/21 had diminished food intake, 6/21 patients had vomiting	16/21	8/21	20/21	8/21	10/15	5/12	14/21
Crohn's disease	21	33.9 (14)	N.A.	8/21 cases had vomiting, 9/21 had diplopia, 2 hearing loss and tinnitus	13/21	17/21	20/21	9/21	15/16	4/7	4/19
Schizophrenia	15	40.7 (9.4)	21.4 (16.3)	6/15 had food related delusions, 2/15 had the delusion of dying, 2/15 had vomiting	13/15	12/15	15/15	12/15	10/10	N.A.	N.A.
Anorexia Nervosa	12	27.8 (13.2)	28.8 (16.8)	4/12 had diplopia, 2/12 refeeding syndrome, 1/12 had severe apathy as presenting sign, 1/12 had acute crying spells as presenting sign	10/12	10/12	9/12	8/12	8/9	N.A.	N.A.
Ulcerative Colitis	10	41.5 (16.5)	26.5 (12)	5/10 cases had vomiting, 3/10 had loss of vision, 2/10 had diplopia, 2 altered auditory processing	5/10	8/10	7/10	4/10	6/6	3/5	2/9
Accidental thiamine deficient infant formula	9	0.5 (0.3)	N.A.	8/9 patients had vomiting, 9/9 cases had infections. 7/9 patients presented with lethargy, 5/9 presented with irritability.	0/9	3/9	9/9	0/9	1/2	N.A.	N.A.

BMI = Body Mass Index in Kg/m^2, N.A. = Not Available, F = Female, M = Male, + = symptom is present, − = symptom is absent, MRI = Magnetic Resonance Imaging, CT = Computed Tomography.

3.5. Progressive symptomatology

WKS often remains undetected because of its relatively rarity when alcohol abuse is not a factor. Usually, when WKS remains undetected and untreated, the number of symptoms increases, and the outcome is worse. This was most clearly presented in the study on obesity surgery: patients developed a progressive clinical course in 31.6%, presenting first with only one symptom progressing into two or three symptoms of the triad. Also, in the systematic review on cancer, there was an average treatment delay of 5.5 days, negatively affecting the outcome. In the study on obesity surgery, and hyperemesis gravidarum, more symptoms of the triad were predictive of more cases developing the chronic phase of WKS.

3.6. Treatment

As can be viewed in Table 1, in almost all reviewed studies, half of the patients received less than 500 mg thiamine per day, resulting in negative long-term outcome. In the study on hyperemesis gravidarum, and the study on obesity surgery, a direct link was evident between doses of thiamine and cognitive outcome.

4. Discussion

Wernicke Korsakoff syndrome (WKS) is a life-threatening neurological disorder caused by thiamine (vitamin B1) deficiency. For the first time we brought together the collection of systematic reports on nonalcoholic WKS to raise clinician's awareness and propagate active treatment of malnutrition in nonalcoholic. Patients often suffer from extreme weight loss and frequent vomiting. Blurred vision was a common presenting sign in one-fourth of the patients. Originally, WKS was described as a triad of ataxia, eye-movement disorders and mental status change, in which mental status change was most frequently present in nonalcoholic WKS. For the three largest groups of nonalcoholic WKS patients, the triad was most often present in hyperemesis gravidarum. MRI was sensitive in nonalcoholic WKS. Treatment typically was too little too late, with most cases, resulting in chronic cognitive disorders, such as Korsakoff's syndrome (KS).

Of interest, in the comparison between nonalcoholic and AUD WKS patients, those with WKS following AUD less frequently had a full presenting triad of symptoms (14%) than nonalcoholic WKS patients (see Table 1) [4]. Additionally, MRI was frequently not sensitive for detection of WKS in AUD (53%) while MRI was often sensitive for nonalcoholic WKS (Table 1) [21]. Moreover, AUD patients were older (average: 57.3 years) than nonalcoholic WKS patients (average: 32.3 years) [22,23], and they were more often male (78.4%) compared to nonalcoholic WKS (Table 1) [22,23]. Because more symptoms of the triad and higher MRI sensitivity reflect late diagnostics in WKS, these findings could indicate lower suspicion of WKS in nonalcoholic patients. In fact, a progression of symptoms with more presenting symptoms over time [10,12], and late recognition (5.5 days delay) [11] were reported in the nonalcoholic WKS literature. Also, the duration of weight loss and vomiting are striking in the nonalcoholic cases [10,12]. It is important to note that nonalcoholic WKS patients were under medical attention, while AUD WKS is frequently not recognized because of self-neglect and care avoidance [4,21]. In this light it is even more shocking that the progression of WKS goes unnoticed for much longer with more devastating neurocognitive consequences.

Two major warning signs that are present in almost all reported cases are extreme weight loss prior to the development of WKS, and vomiting. In the reviewed cases weight loss is usually a sign of insufficient nutritional intake, or nutrients being lost in the body. A large number of conditions can lead to diminished intake, or the need for an increased dosage of thiamine and other nutrients. Other presenting signs of thiamine deficiency are a loss of appetite, fatigue, irritability, reduced reflexes, tingling sensations in arms and legs, blurred vision, diarrhea, nausea and vomiting [1,5]. In case of rapid weight loss, or any of the above mentioned symptoms, it is important to administer thiamine to reduce the risk for WKS.

The most frequently reported cases in this review are patients with hyperemesis gravidarum. In hyperemesis gravidarum, the body rapidly loses weight due to loss of nutrients in both mother and infant. Classic hyperemesis gravidarum patients have been submitted to the hospital for a prolonged time and are bedridden. The large number of reported cases ($n = 177$) shows that even within hospitals it is not commonly known that parenteral thiamine injections are necessary in preventing the development of WKS [10]. Unfortunately, a progressive clinical course with a progression to a full triad of symptoms, including sensitive MRI for subcortical damage, and inadequate thiamine treatment following detection of WKS are very common within this population. Half of the fetuses, and 5% of the mothers were lost due to WKS. More than half of the patients with WKS develop chronic cognitive issues [10]. Moreover, both the full triad of symptoms, and the individual symptoms of WKS were most pronounced in this group.

Cancer can take many forms, but specifically haematologic malignancies, because of high cell turnover, and gastrointestinal malignancies, due to malnutrition and malabsorption, form a risk for the development of WKS. In the review conducted by Isenberg-Grzeda and colleagues on cancer and 129 patients with WKS [11], only 13% of the first authors of the included reports were oncologists, suggesting that it is not common knowledge that cancer can lead to severe thiamine deficiency and WKS. Around one-fifth of the patients were diagnosed at autopsy. The authors recommend that clinicians should actively supplement thiamine in patients at risk for WE. Also, clinicians may rely too much on the classic triad of symptoms, while often only an altered mental status can be indicative of WKS [9]. Of the three largest groups in this study, the triad was least present in this group compared to hyperemesis gravidarum and bariatric surgery.

Bariatric surgery is intended to help obese patients attain a healthier body weight. By restricting the size of the stomach or gastrointestinal tract and stomach however, the ability to absorb thiamine is vastly reduced. In most reports on WKS following bariatric surgery [12], patients developed vomiting before onset of WE. Importantly, patients remained at risk for WKS, because complications later on could also lead to WKS after bariatric surgery (up to 10+ years after the procedure was carried out). The non-compliance in the bariatric WKS patients was high (10.3%), suggesting that specifically in bariatric patients, information regarding proper nutrition should be provided. Moreover, in bariatric patients losing too much weight too quickly, prophylactic parenteral thiamine treatment is necessary to prevent the development of WKS. In bariatric patients, a progressive clinical course of WKS was often observed, directly resulting in more chronic KS patients.

Psychiatric disorders can be accompanied by substantial dietary restrictions, because of the fear of gaining weight in anorexia nervosa [18], losing interest in food in depression [19], and food related delusions or hallucinations in schizophrenia [17]. In most cases, an enormous weight loss transpired prior to the development of WKS, co-occurring with social isolation, and sometimes somatic conditions complicating the psychiatric disorder. For ambulatory psychiatric patients that avoid care and lose weight, it is of particular relevance that clinicians supply oral thiamine to non-vomiting patients and parenteral thiamine to vomiting ones. Of interest, in the anorexia nervosa literature [18], there was an increased risk of inducing WKS by giving glucose to patients without proper thiamine support.

One systematic review by Scalzo and colleagues (2014) that was not included in this report because symptomatology was not directly included in this review, included all 623 nonalcoholic WKS case studies published between 1867 and 2014 [24]. In their study, 62% of the cases were reported after 1990, possibly because of greater awareness and understanding of WKS. One of their findings was that not only bariatric surgery and cancer, but also other gastrointestinal problems such as obstructions (25 cases) and pancreatitis (10 cases) could lead to WKS.

They also reported 29 cases on WKS following intravenous feeding or hyperalimentation, 11 cases following dialysis and 10 cases following HIV/AIDS. Importantly, 90 patients had other, not predefined nonalcoholic causes of WKS. These results suggest that the possible causes of WKS are much broader than the reported cases in our review.

In all case series [10–19], the number of reported cases has been rising dramatically in the last ten years. It is possible that recognition of WKS has improved, but it is also possible that more patients develop WKS. One reason to assume that more patients are developing WKS is that society is increasingly becoming more individualized, restricting the care for the most vulnerable. Also, global health costs are rising, possibly resulting in less attention for malnutrition and its consequences [3,4].

The large challenge for the attending physician is to spot the risks and initial symptoms of WKS on time. This early signaling is severely complicated by the primary symptoms of the underlying disease, in particular when this is psychiatric or cancer related. Any sign of delirium, confusion, cognitive defect or change in mobility in an admitted patient that has lost weight or is at risk for malnutrition due to low weight should alarm clinicians for treatable WKS. According to the Royal College of Physicians (RCP), parenteral thiamine should be given 500 mg three times daily until symptoms of acute WKS resolve. The European Federation of Neurological Societies (EFNS) recommends 200 mg three times per daily until symptoms resolve. Because of the dose-response relationship, we recommend to follow the RCP guidelines [20,22,25].. The treatment is lifesaving and has the potential to reverse this acute neuropsychiatric syndrome. It is recommended to have a high suspicion of WKS in all patients that lose weight, and in particular in cancer patients on specific chemotherapy drugs which can impair the action of thiamine at a cellular level [26].

This study has some limitations. Case studies can have multiple biases, such as publication bias and detection bias [3]. Many patients with WKS are detected, but not reported on in case studies. It is therefore likely that WKS in nonalcoholics is a far greater problem than assumed based on the reported case descriptions. Moreover, the quality of case reports on WKS is variable, and the knowledge regarding the course of symptoms, best treatment practice, and outcome of WKS is generally unknown in many case reports. Finally, we aimed to review recent systematic investigations into WKS, but did not review all potential conditions leading to WKS. For example, systemic conditions, but also famine, gastrointestinal issues, chronic diuretic therapy, pyloric stenosis, and a multitude of other conditions were not reviewed here. We assume that also in these conditions, losing weight, vomiting, and not eating a balanced diet can cause WKS.

5. Conclusion

In conclusion, nonalcoholic WKS is atypical, but should be nonexistent when patients at risk for malnutrition are prophylactically treated with parenteral thiamine. Oral thiamine is not sufficient in preventing WKS in patients that vomit or lose weight. Patients with nonalcoholic WKS are relatively young, and females are overrepresented. Even babies and children can develop WKS because of improper nutrition. Drastic weight loss (>20% of the patient's body weight within months) requires parenteral thiamine treatment of 500 mg, three times a day.

Declaration of Competing Interest

There are no conflicts of interest.

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The corresponding author confirms that he has the full access to all the data in the study and has the final responsibility for the decision to submit for publication.

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