Psychosomatics 2016:57:624–633

Original Research Reports

Severe Infections are Common in Thiamine Deficiency and May be Related to Cognitive Outcomes: A Cohort Study of 68 Patients With Wernicke-Korsakoff Syndrome

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Background: *Wernicke encephalopathy can have different clinical outcomes. Although infections may precipitate the encephalopathy itself, it is unknown whether infections also modify the long-term outcome in patients developing Korsakoff syndrome.* **Objective:** *To determine whether markers of infection, such as white blood cell (WBC) counts and absolute neutrophil counts in the Wernicke phase, are associated with cognitive outcomes in the end-stage Korsakoff syndrome.* **Method:** *Retrospective, descriptive study of patients admitted to Slingedael Korsakoff Center, Rotterdam, The Netherlands. Hospital discharge letters of patients with Wernicke encephalopathy were searched for relevant data on infections present upon hospital admission. Patients were selected for further analysis if data were available on WBC counts in the Wernicke phase and at least 1 of 6 predefined neuropsychological tests on follow-up.* **Results:** *Infections were reported in 35 of 68 patients during the acute phase of Wernicke-Korsakoff syndrome—meningitis (1), pneumonia (14), urinary tract infections (9), acute abdominal infections (4), sepsis (5) empyema, (1) and infection "of unknown origin" (4). The neuropsychological test results showed significant lower scores on the Cambridge Cognitive Examination nonmemory section with increasing white blood cell counts (Spearman rank correlation, $\rho = -0.34$; 95% CI: −0.57 to −0.06; 44 patients) and on the "key search test" of the behavioral assessment of the dysexecutive syndrome with increasing absolute neutrophil counts ($\rho = -0.85$; 95% CI: −0.97 to −0.42; 9 patients).* **Conclusions:** *Infections may be the presenting manifestation of thiamine deficiency. Patients with Wernicke-Korsakoff syndrome who suffered from an infection during the acute phase are at risk of worse neuropsychological outcomes on follow-up.*

(Psychosomatics 2016; 57:624–633)

Key words: thiamine deficiency, infection, Wernicke-Korsakoff syndrome, memory disorders, executive function, critical illness.

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INTRODUCTION

Acute Wernicke encephalopathy can have different clinical outcomes—full recovery, various degrees of cognitive deficits, coma, or death. Mortality in the acute phase is mostly attributable to sepsis that frequently originates from the lungs, liver cirrhosis, and the effects of irreversible thiamine deficiency.[1] Wernicke encephalopathy and Korsakoff syndrome are considered to be the different stages of the same disorder following vitamin B_1 (thiamine) deficiency, which is called Wernicke-Korsakoff syndrome (WKS).

Background Information on WKS

Wernicke encephalopathy is characterized "classically" by ocular motility abnormalities—external ophthalmoplegia or nystagmus or both, ataxia affecting primarily the gait, and mental confusion or delirium.[2] As Wernicke encephalopathy is essentially a clinical diagnosis warranting prompt treatment, presumptive treatment should not be delayed pending the results of diagnostic procedures. Moreover, serum thiamine levels may be a poor measure of thiamine status, and results of brain magnetic resonance imaging may be found to be normal in some cases of Wernicke encephalopathy.

If high-dose parenteral thiamine is not given urgently, the biochemical abnormalities that thiamine deficiency causes can lead to irreversible brain damage.[2] Brain lesions in Wernicke encephalopathy are commonly found in the thalamus, mammillary bodies, subependymal structures (along the third and fourth ventricles and the aqueduct), and the inferior olivary nuclei.[3] The brain damage may lead to death, with mortality rates of 17−20% being reported, or in 85% of survivors, to the chronic Korsakoff syndrome, characterized by short-term memory loss, but with relative reservation of intellectual functions.[2] In postmortem studies, Wernicke encephalopathy occurred in chronic alcoholics at a frequency of 12.5%; in the population as a whole, the figure is ~1.5%.[3] However, Wernicke encephalopathy is widely underdiagnosed, so these figures are likely to represent an underestimate of the true prevalence.[2] The work of Harper et al. demonstrated that the diagnosis of Wernicke encephalopathy was only made clinically in 16% of cases before autopsy.[4] In a further review of pathologic studies, only 10% of patients with Wernicke encephalopathy had the full classical triad of clinical signs, 23% had ataxia, 29% had ocular signs, and 82% presented with mental changes (i.e., confusion, drowsiness, obtundation, precoma, and coma).[4]

The diagnosis of the acute phase of WKS can be made according to the operational criteria of Wernicke encephalopathy developed by Caine et al.[5] The diagnostic criteria are as follows: (1) dietary deficiency, (2) oculomotor abnormalities, (3) cerebellar dysfunction, (4) and either altered mental state or mild memory impairment. For the Wernicke encephalopathy diagnosis, patients should fulfill at least 2 of the criteria. The diagnosis of chronic Korsakoff syndrome can be made according to the DSM-5 criteria for major neurocognitive disorder of the confabulating-amnestic type.[6] The Korsakoff syndrome diagnosis should be confirmed by extensive neuropsychological testing after at least 6 weeks of sobriety.

In general, Korsakoff syndrome is characterized by severe anterograde and, to a lesser extent, retrograde amnesia for declarative knowledge.[7] Moreover, many patients have executive function deficits, such as problems with initiative, planning, organizing, and regulating behavior.[8] Patients themselves are not tuned into these problems because they have limited awareness of their illness (anosognosia). Although patients with Korsakoff syndrome can exhibit confabulations, these are also found in other neurologic conditions, and the intensity of confabulations may vary from one patient to another.

Our group represented a specialized population of patients being referred to Slingedael Korsakoff Center. The total number of patients with Korsakoff syndrome in our region, that is, the city of Rotterdam and its surrounding areas, is unknown. The Rotterdam Public Health Service (GGD Rotterdam-Rijnmond) made an estimation of 275–450 patients with Korsakoff syndrome (corresponding with a prevalence of 3.0–4.8 patients per 10,000 inhabitants) living at home, in homeless shelters, in residual care homes or staying in alcohol clinics, general/psychiatric hospitals, and other care facilities, in Rotterdam and surrounding areas.[9]

Infections and Thiamine Deficiency

Critically ill patients may present with thiamine deficiency or develop this deficiency during their acute illness.[10] Systemic infection is often revealed by or associated with brain dysfunction, and Wernicke

encephalopathy is one of the main differential diagnoses of infection-related encephalopathy.[11]

According to pediatric literature, infections can be a heralding sign of severe thiamine deficiency—as was shown in infants with thiamine deficiency presenting with infections and lactic acidosis. Fattal-Valevski et al. described 9 infants with thiamine deficiency caused by a soy-based infant formula lacking thiamine. In these children, the appearance of thiamine deficiency symptoms roughly coincided with the appearance of fever or infection. The early clinical symptoms were nonspecific, including, among others, vomiting, anorexia, lethargy, irritability, and developmental delay, and were sometimes considered to be manifestations of concomitant infections, teething, or food intolerance.[12]

Having an infection can increase the use of thiamine and may precipitate Wernicke encephalopathy in patients with marginal thiamine reserves.[13,14] Although many studies described the transition of Wernicke encephalopathy to Korsakoff syndrome,[4,7,15] the possible role of systemic infections in this transition is not clear.

Aim of the Study

Based on the relationship between thiamine deficiency and infections, we hypothesized that infections may be associated with the severity of cognitive deficits in patients with WKS (Figure 1).[16,17] The research questions were as follows: how common were infections in the initial phase of WKS? Were white blood cell (WBC) counts and absolute neutrophil counts related to the cognitive outcomes?

METHOD

Study Design and Subjects

In a retrospective, descriptive cohort study, we included patients admitted to Slingedael Korsakoff Center. From February 1, 2012, to March 1, 2014, 64 patients admitted to the observation department were evaluated for inclusion and 96 patients of the residential care departments at the set date of March 1, 2014. The study was approved by the Medical Ethics Review Committee of the Utrecht University Medical Center (UMC Utrecht), Utrecht city, the Netherlands (reference number 16-133/C), with a waiver of informed consent. Inclusion criteria for the present analysis were a diagnosis of WKS with complete data on white blood count during the preceding acute phase and the availability of predefined neuropsychological test results during follow-up, including cognitive screening tests or more extensive neurocognitive tests or both. Data collection involved the patients' age, sex, body mass index, alcohol use, infection diagnoses, and neuropsychological test scores. Laboratory results consisted of routine biochemical and hematological testing from the previous hospital setting. Developing WKS symptoms were categorized as "drowsiness,"[18] "confusion," "walking disability," or "collapse" if the patient was found on the floor. Reasons of exclusion from the present analysis are summarized in Figure 2.

Infection Diagnoses

In the study, "infections" refer to diagnoses listed in the patients' hospital discharge letters. We reviewed these letters for diagnoses of inflammatory diseases (e.g., inflammation of the lungs/pneumonia and urinary tract infections)[1,2] that were present upon admission in the acute phase, according to the reports on the diagnostic workup including blood tests, chest films, and bacterial cultures or any other information. We extracted data on body temperature, heart rate, and blood pressure, if available.

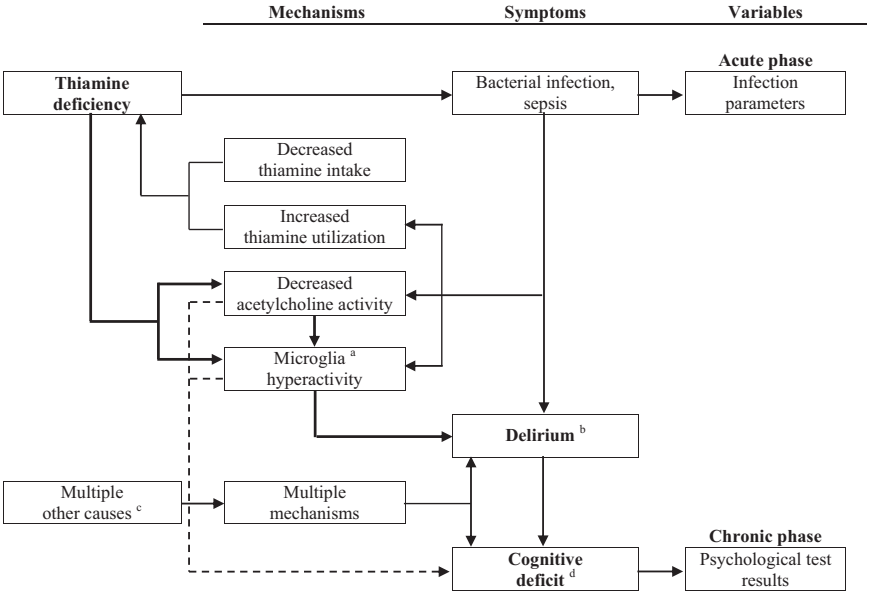
Neuropsychological Tests

If available, we recorded the results of 6 predefined neuropsychological tests as an element of extensive neuropsychological examinations. Patients were administered the Cambridge Cognitive Examination (CAMCOG)—a cognitive screening task developed to detect dementia.[19] Based on earlier research, the scores on this screening instrument can be divided into a memory section that is particularly sensitive to Alzheimer dementia and a nonmemory section that is sensitive to nonmemory forms of cognitive decline.[20] Furthermore, patients were administered the mini-mental state examination and cognitive screening test (CST-20), both are cognitive screening instruments

[1] Inflammation: a pathologic process characterized by injury or destruction of tissues caused by a variety of cytologic and chemical reactions. It is usually manifested by typical signs of pain, heat, redness, swelling, and loss of function (MeSH database; www.ncbi.nlm.nih.gov).

[2] Infection: invasion of the body by micro-organisms that can cause pathologic conditions or diseases.

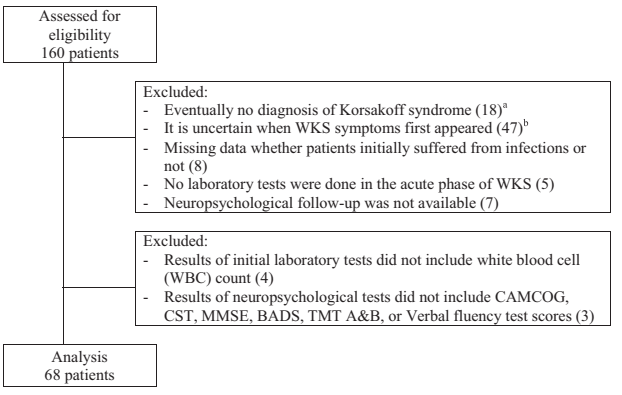
FIGURE 1. **Interdependency of Infections and Wernicke-Korsakoff Syndrome. (A) Microglial Cells of the Brain. Wang and Hazell Observed Induction of Microglial Activity in Their Thiamine-Deficient Rodent Model.[16] Based on an Hypothesis of Van Gool et al., Systemic Infections May Cause Microglial Hyperactivity Leading to a Delirium.[17] (B) Delirium due to Thiamine Deficiency = Wernicke Encephalopathy. (C) Electrolyte Disorders, Alcohol Withdrawal, Hepatic Failure, Renal Failure, Brain Injury, etc. (D) Neurocognitive Disorder due to Thiamine Deficiency = Korsakoff Syndrome.**



sensitive for dementia.[21,22] Patients were administered the behavioral assessment of the dysexecutive syndrome (BADS)—an ecologically valid test battery for executive problems. This battery consists of 6 tasks that index rule-shifting and response-inhibition (rule-shift test), planning and problem-solving (action-program test), planning and monitoring (key search test), guessing (temporal judgment), planning and strategy use (zoo map test), and unstructured planning and controlling (six element test).[23] Patients were administered the Trail-Making test to index divided attention and cognitive flexibility.[24] Moreover, patients were administered the verbal fluency test to index expressive language and working memory functioning.

Executive dysfunctions, as well as memory impairments, are defining characteristics of Korsakoff syndrome.[7,25] Because of the divergent clinical outcome regarding cognitive disturbances in patients with Korsakoff syndrome,[26] we chose to separately examine the nonmemory section of the CAMCOG and the subtests of the BADS, including the "key search test" among others.

FIGURE 2. **Flowchart of Patient Selection. WKS = Wernicke-Korsakoff Syndrome; CAMCOG = Cambridge Cognitive Examination; MMSE = Mini-Mental State Examination; CST = Cognitive Screening Test; BADS = Behavioral Assessment of the Dysexecutive Syndrome; TMT = Trail Making Test A&B. (A) Dementia (9 Patients), Acquired Brain Injury (3), Hepatic Encephalopathy (1), Minimal or Atypical Cognitive Symptoms (1), Others (4). (B) No Clear Starting Point of the Mental Symptoms: No Data (24 Patients), a Single Episode of Wernicke Encephalopathy or Korsakoff Syndrome Lacking Details (10), Intermittent Episodes of Wernicke Encephalopathy With Current Episode of Korsakoff Syndrome (9), and Gradual Deterioration Over Time (4).**



Statistical Tests

The unpaired Student *t* test was used to compare laboratory results of patients with and without infections. Associations between WBC count and cognitive scores were explored with plots and Spearman Rho coefficients with 95% CI. The statistical analyses were conducted with SPSS, version 21.

RESULTS

Patient Characteristics

Patient characteristics are shown in Table 1. All patients had at least 2 or more symptoms according to the DSM-5 diagnostic criteria of alcohol use disorder.[6] Malnutrition mostly because of self-neglect was recorded in 55 of 68 patients, if the patient had not been eating well for the past few months, and sometimes not eating at all for several days/weeks. The WKS symptoms developed within median 3.5 days (interquartile range: 1−14 days) before hospital admission. Symptoms were drowsiness in 12 (18%) patients, confusion in 48 (71%) patients, walking disability in 19 (30%) patients, and collapse in 8 (12%) patients.

Infections and Laboratory Results

Infections were present in 35 of 68 patients during the initial phase of WKS. Focus was absent in 4 of 35 patients. The main sites of the infections are given in Table 2. In 2 of 35 patients, the infections occurred *after* the first week of hospital admission. In routine biochemical and hematological testing, no statistically significant differences were found between patients with and without infections, except for differences of infection parameters. However, clinically relevant laboratory abnormalities were seen in both groups, for example, anemia, electrolyte disorders, renal dysfunction, liver dysfunction, and vitamin deficiencies (Appendix Table A1).

Neuropsychological Test Scores

The time period between laboratory assessment in the acute phase of WKS and neuropsychological assessment in the chronic phase of WKS was median 4.5 months (interquartile range: 2.5−8 months). CAMCOG total scores were available in 45 of 68 patients, CAMCOG nonmemory scores in 44 of 68 patients, Mini-Mental State Examination scores in 60 of 68 patients; the other numbers are given in Table 3. Overall,

TABLE 1. Patients Referred to Slingedael Korsakoff Center

Characteristics	No. (%)	Mean (SD)
Age (year)		
Male	132	59 (8)
Female	28 (18%)	58 (9)
BMI (kg/m^2)		
Male	119*	23.1 (4.1)
Female	25*	23.0 (5.4)
Alcohol use (mL/day)†		
Male	69‡	240 (170)
Female	16‡	200 (103)
Prior diagnostic setting§		
Inpatient, general hospital	99 (62%)	
Inpatient, mental health care	26 (16%)	
Outpatient, ambulatory	32 (20%)	
Missing data	3 (2%)	
Referred to Slingedael by‖		
General hospital	62 (39%)	
Mental health care¶	61 (38%)	
Other#	37 (23%)	

BMI = body mass index; No. = number of patients.

* Missing data in the other male/female patients.

† Quantity of pure alcohol (mL/day): beer 250 mL = 12.5 mL pure alcohol, wine 100 mL = 12 mL pure alcohol, liquor 35 mL = 12.25 mL pure alcohol.

‡ Unspecified as "alcohol abuse" in the other patients.

§ Diagnostic setting in which Korsakoff syndrome was diagnosed or strongly suggested.

‖ Following hospitalization, patients may have been admitted to a care facility elsewhere or discharged home, before being referred to Slingedael Korsakoff Center.

¶ Psychiatric hospital, psychiatric department, alcohol clinic, ambulatory mental health care.

Nursing home, GP, homeless shelter, and other.

TABLE 2. Infection Diagnosis in Patients Referred to Slingedael Korsakoff Center

Pneumonia (14 of 35 patients) complicated by or in combination with empyema (1 patient), sepsis (1), urinary tract infections (1), meningitis/double-sided pneumonia (1), and recurrent pneumonia (1)
Urinary tract infections (8 of 35) complicated by sepsis (2) and possible pneumonia (1)
Acute abdominal infections (4 of 35): peritonitis (2), pancreatitis (1), and enteritis (1: Norovirus)
Sepsis of unknown origin (2 of 35)
Infection of unknown origin (4 of 35)
Other (3 of 35): esophagitis (1) and skin/ wound infections (2).

TABLE 3. Neuropsychological Test Scores Subdivided by Initial Infection Status[‖]

Results, Mean (SD)	No.	With Infection	No.	Without Infection	Ref Value	ρ[†] WBC	95% CI	ρ[‡] ANCs	95% CI
CAMCOG total score	28	74.8 (10.5)	17	76.1 (9.6)	76–105	−0.17	−0.44 to 0.12	0.04	−0.60 to 0.65
Nonmemory section	27	53.1 (6.1)	17	57.2 (8.3)		−0.34	−0.57 to −0.06*	−0.27	−0.77 to 0.43
MMSE	33	21.9 (4.8)	27	21.8 (3.8)	24–30	−0.05	−0.29 to 0.20	0.10	−0.38 to 0.54
CST-20	9	13.1 (3.3)	14	11.8 (4.9)	16–20	−0.05	−0.44 to 0.32	N/A	
BADS total score	17	12.4 (3.3)	13	12.2 (4.2)	13–24	−0.20	−0.57 to 0.22	−0.24	−0.51 to 0.78
BADS Key search test	20	1.4 (1.4)	17	2.0 (1.4)		−0.26	−0.55 to 0.08	−0.85	−0.97 to −0.42**
TMT A, percentile	20	15 (17)	25	11 (23)	>8	−0.04	−0.33 to 0.27	−0.17	−0.63 to 0.37
TMT B[¶], percentile	19	18 (24)	25	12 (22)	>8	0.05	−0.26 to 0.33	0.05	−0.48 to 0.55
Verbal fluency test[§]	26	14.8 (6)	28	16.5 (7)	>14	−0.23	−0.49 to 0.05	−0.08	−0.55 to 0.43

BADS = Behavioral Assessment of the Dysexecutive Syndrome consisting of 6 subtests; CAMCOG = Cambridge Cognitive Examination; CST-20 = Cognitive Screening Test; MMSE = Mini-Mental State Examination; N/A: ANC and CST-20 tests were reported in 4 patients only; No. = number of patients; Ref value = reference value of neuropsychological test scores; TMT = Trail Making Test A and B.

[‖] Infections occurred in 35 of 68 patients.

[†] Spearman rank correlation coefficient (Rho) was calculated from white blood cell (WBC) counts and neuropsychological test scores, with 95% CI.

[‡] Data on absolute neutrophil counts (ANCs) were available in 18 patients or less.

* $P < 0.05$.

** $P < 0.01$. Interpretation of strength of correlations: 0–0.15 very weak, 0.15–0.25 weak, 0.25–0.40 moderate, 0.40–0.75 strong, and 0.75–1 very strong. Negative coefficients reflect negative correlations, that is, when test scores tend to decrease as WBC counts (or ANCs) increase.

[¶] Ceased in 8 of 44 patients, resulting in 0 percentile score.

[§] Category fluency test, naming animals in 1 minute.

the correlation coefficient calculated from WBC counts and neuropsychological test scores was negative, indicating more impairments on follow-up with increasing WBC counts in the acute phase, for almost all cognitive test scores (Table 3). The correlation was statistically significant for the nonmemory section of the CAMCOG ($\rho = -0.34$; 95% CI: −0.57 to −0.06; 44 patients). Rho calculated from absolute neutrophil counts and neuropsychological test scores was significant for the "key search test" of the BADS ($\rho = -0.85$; 95% CI: −0.99 to −0.44; 9 patients, Appendix Figure A1).

Other Measurements

There were no significant differences between patients with and without infections for body temperature, heart rate, or blood pressure, although in both groups clinically relevant abnormalities were found—the initial body temperature was 85.6–101.1°F, heart rate 70–126 beats/min, and systolic blood pressure 89–175 mm Hg, according to the hospital discharges letters (< 30 patients).

DISCUSSION

In the acute phase of the alcohol-related WKS, serious infections were present in our patient group.[3] In the end-stage Korsakoff syndrome, almost all neuropsychological test results were consistently worse in subjects who had experienced an infection at presentation. This association was significant for lower outcomes of the CAMCOG nonmemory section with increasing WBC counts, and of the "key search test"' of the BADS with increasing absolute neutrophil counts. Thus, differences in neuropsychological test scores were mainly observed in only 2 nonmemory subtests of the 6 preselected neuropsychological tests. These results might give some indication that delirium and infections are associated with worse cognitive outcomes in WKS.

In general, infections may be a marker for more severe malnutrition. That more severe malnutrition increases risk for infection is well known and not likely specific to WKS. In the study of Fattal-Valevski et al., however, the outbreak of infantile beriberi and Wernicke encephalopathy has been associated with the consumption of a nondairy soya-based infant formula. In this outbreak, 11 of 16 children with clinical symptoms of thiamine deficiency had fever or infections.[12]

Our patients had been admitted to the hospital for various reasons, such as confusion, drowsiness, or

[3] "Infections" refer to diagnoses listed in the patients' hospital discharge letters.

collapse, and were eventually identified as having WKS. Infections may have been incidental comorbid findings. Based on the literature, however, we assumed that comorbid infections can be regarded as a symptom of thiamine deficiency[12,14] and a complicating factor in already marginalized thiamine reserves.[13,14]

Thiamine Deficiency and Sepsis

Sepsis was reported in 5 of the 35 patients with infection. Initial low body temperature was observed both in patients with and without infections. This can probably be explained by previous observations that thiamine deficiency and sepsis both may present as hypothermia. However, hypothermia in thiamine deficiency might be masked by infections, in other cases.[27] Remarkably, infection "of unknown origin"' was reported in 4 of 35 patients. We wondered whether these cases might reflect unidentified sepsis of unknown origin.

Recent Literature on Thiamine Deficiency and Sepsis

Thiamine deficiency may be highly prevalent in patients with sepsis as described in a study examining serum thiamine, oxidative stress,[4] and hospital mortality in adult patients with septic shock.[28] Of 108 patients, 77 (71%) had thiamine deficiency, defined as serum thiamine concentrations of <16 ng/mL (reference range: 16−48 ng/mL). Serum thiamine levels were not associated with the hospital mortality—although other studies of critical illness in adults and children showed that absolute or relative thiamine depletion was associated with an almost 50% increase in mortality.[29] Also, serum thiamine levels were not associated with protein carbonyl concentrations in serum samples, as markers of oxidative stress or protein damage.[4,5] In an another study, 6 (20%) of 30 patients with sepsis had absolute thiamine deficiency, defined as serum thiamine concentrations of $\leq$ 9 nmol/L.[10] Furthermore, 3 of these patients had an absolute thiamine deficiency upon presentation and 3 patients developed an absolute thiamine deficiency within 72 hours, with thiamine levels measured at intervals of 24 hours. None of the 30 control patients (0 of 30, 0%) showed absolute thiamine deficiency. In a mouse model of sepsis, de Andrade et al. concluded that thiamine-deficient food was associated with oxidative stress and inflammatory response changes.[30] The septic condition included cecal ligation and puncture, thus exposing the abdominal cavity to fecal contamination. Total WBC counts and absolute neutrophil counts were the highest in the septic condition (cecal ligation and puncture) with thiamine-deficient food, but differences were significant for mononuclear cell counts. Interleukin-6 (IL-6) blood levels tended to be higher in cecal ligation and puncture. Higher liver 4-hydroxy 2-nonenal (4-HNE; $C_9H_{16}O_2$) levels were associated with oxidative stress in thiamine-deficient food.

Cognitive Outcomes

Earlier research on the nonmemory section of the CAMCOG indicated that the more advanced cognitive decline after the initial memory disturbance in progressive forms of dementia was better predicted by the nonmemory section than the memory section of the CAMCOG.[19] The current finding of a negative relationship between the nonmemory section of the CAMCOG and infection parameters, therefore, is likely to suggest that in addition to the severe memory disturbance that are common in patients with WKS, the patients who have had more serious infections in the initial phase display more severe cognitive decline in other cognitive domains than memory, such as executive functioning and speed of processing.

How important is it that the CAMCOG nonmemory section differed by mean 4.1 points in the patients with or without infection? In the general population, scores on the CAMCOG nonmemory section differed by 5 points in the interquartile range (interquartile range: 25th–75th percentile of scores) in a selection of 2832 nondemented participants aged 65–69 years.[31] In our patient group, the interquartile range was 69–81 points and 51.5–58 points, respectively, for the CAMCOG total scores and CAMCOG nonmemory scores. If corrected for age and educational level, mean CAMCOG scores (total score and nonmemory score) in our patient group were lower than the first percentile scores in the general population.[32] Reference values of the other

[4] Oxidative stress: a disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential damage. Indicators of oxidative stress include damaged DNA bases, protein oxidation products, and lipid peroxidation products.

[5] Protein carbonylation: the appearance of carbonyl groups, such as aldehyde or ketone groups, in proteins because of several oxidative modification reactions.

neuropsychological test scores are given in Table 3. For the subtests of the BADS, no reference values are available.

New Questions

Along with these results, there are, however, a number of outstanding questions requiring further consideration. These questions include the severity of thiamine deficiency and the nature and strength of the effect of systemic infection on cognitive functioning: (1) If indeed there is a correlation between infection and worse outcomes in WKS, then can it be said that infection itself is linked to a poorer prognosis, (2) or is it that the infection is a marker of more severe degrees of thiamine deficiency? (3) Might there be a bottom effect, as infection would use already depleted thiamine stores? (4) Can possible cognitive effects of systemic inflammation in WKS be interpreted in terms of a differential vulnerability of brain areas involved in executive functioning and those involved in memory function? (5) Are worse cognitive outcomes more specifically related to septic conditions or, for example, endotoxins of gram-negative bacteria?

Strength and Limitations

We provided the first direct indication that the systemic infections in the acute Wernicke phase might be associated with the long-term cognitive deficits in WKS. The observations of this study may bring more awareness to the relationship between infections and thiamine deficiency and contribute to improving early diagnosis and treatment of WKS. The present study has several limitations. First, our data were collected retrospectively, and this may have affected the quality of the data in some respects. Selection bias may have been introduced by diagnostic conclusions relying on limited data that were retrieved from the patients' hospital discharge letters, rather than from their full medical files. There were limited data regarding a complete set of relevant parameters of infection. Metabolic acidosis was not documented, as thiamine deficiency and sepsis may be associated with various degrees of acidosis.[10,12,33] Secondly, possible covariates of WBC counts, for example, smoking, amount of stress, or thiamine deficiency itself, were not taken into account. It is not yet clear to what extent elevated WBC counts reflect the presence of infections in WKS in those cases where no infections were found. Owing to lack of detailed data, no analysis could be made of severity of alcohol dependence, severity of thiamine deficiency, severity of infections and subsequent inflammation, critical illness, or number of intensive care admissions.

CONCLUSIONS

In the literature, there is limited information available regarding the incidence of infections in the initial stages of WKS or the effects of inflammation on the ultimate Korsakoff syndrome. Infections can be a heralding sign of severe thiamine deficiency and Wernicke encephalopathy. Severe infections were common during the Wernicke phase of Korsakoff patients admitted to Slingedael Korsakoff Center, Rotterdam. Although the results have to be interpreted with considerable caution, our data provided a first direct indication that infections in the acute phase might be associated with the long-term cognitive deficits in WKS.

Consequenses for Daily Practice

The overall message is that the empirical treatment of infections in a confused alcoholic patient should include adequate thiamine supplementation. However, it is important not just to focus on the importance of thiamine supplementation in malnourished alcoholic patients, but in any patient who is malnourished for any reason. Although WKS is far more commonly reported in the context of alcohol, there is now established evidence for WKS in malnourished patients without alcohol, such as in anorexia nervosa, hyperemesis gravidarum, postgastric surgery,[34–36] and in several cases with serious comorbid infections.[37,38]

Suggestions for Future Research

The interrelationship of infections and thiamine depletion may represent a relevant area for further research in critically ill patients.[29,39] Early and adequate thiamine supplementation could be helpful to self-neglecting alcoholic patients presenting with infections, confusion, drowsiness, or walking disability.[40] The effects of thiamine administration on infection parameters, including cytokines and

inflammatory markers in thiamine-deficient patients, are not yet known and may be subject to future research.

Disclosure: The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

APPENDIX A. SUPPLEMENTARY INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psym.2016.06.004.

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