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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.*

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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