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Complete Recovery from Undertreated Wernicke-Korsakoff Syndrome Following Aggressive Thiamine Treatment

THOMAS PAPARRIGOPOULOS, ELIAS TZAVELLAS, DIMITRIS KARAISKOS, ANASTASIOS KOUZOUPIS and IOANNIS LIAPPAS

Athens University Medical School, First Department of Psychiatry, Eginition Hospital, Athens, Greece

Abstract. *Background: Wernicke-Korsakoff syndrome (WKS) is a neuropsychiatric condition which results from thiamine deficiency, most commonly due to alcohol abuse. The prognosis of WKS is poor and its outcome depends mainly on prompt treatment. Case Report: A 52-year-old male with a ten-year history of heavy alcohol abuse was admitted in hospital and treated for WKS. Ataxic and oculomotor symptoms promptly reversed following standard treatment but no change was observed in higher mental functioning. Although the protracted WK symptoms made the patient's improvement unlikely, aggressive treatment with thiamine (600 mg/day orally and 300 mg/day intramuscularly) fully reversed the condition within two months. Conclusion: Even though prolongation of undertreatment of WKS typically precludes significant improvement of symptoms due to irreversible damage of the brain, at least in some cases, higher thiamine doses (over 500 mg/day) for a longer period (at least three months) than usually recommended should be tried.*

Wernicke-Korsakoff syndrome (WKS) is a relatively common and potentially lethal neuropsychiatric condition which results from thiamine deficiency, usually due to alcohol abuse. Wernicke's encephalopathy (WE) is the acute phase associated with high mortality and usually presenting with a typical clinical pattern, *i.e.* oculomotor abnormalities, ataxic symptoms, and mental status changes. Korsakoff's syndrome (KS) is the subsequent chronic form of the disorder, which involves a severe impairment in memory and relatively minor deficits in other cognitive functions. The prognosis of WKS is poor and its outcome depends mainly on prompt treatment (1-3). The present case study describes the second published report (4) of complete recovery from an undertreated WKS following delayed aggressive thiamine treatment.

Correspondence to: Thomas Paparrigopoulos, MD, Assistant Professor of Psychiatry, Athens University Medical School, First Department of Psychiatry, Eginition Hospital, 74, Vas. Sofias Ave. 115 28 Athens, Greece. Tel/Fax: +30 2107289324, e-mail: tpaparrig@med.uoa.gr

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Case Report

A 52-year-old male with a ten-year history of heavy alcohol abuse (wine, >3 l/day) was transferred from a neurology department to our drug and alcohol addiction clinic for the management of persisting behavioral disturbances and cognitive deterioration. In the neurology department he had been admitted for symptoms of WE, *i.e.* severe postural and gait ataxia, horizontal nystagmus, bilateral abducens palsy and mental confusion, which had been preceded by a one-month period of binge drinking, severe undernourishment and persistent vomiting. Following a one-month hospitalization, initial intravenous feeding, re-hydration, restoration of electrolytic balance, and treatment with thiamine (100 mg/day, intramuscularly), vitamin B6 (2700 mg/day orally and 350 mg/day *i.m.*), vitamin B12 (1.2 mg/day orally, 1 mg/day *i.m.*, and 1000 μg/week *i.m.*), vitamin E (150 mg/day orally), vitamin A (75000 IU/day orally), folic acid (10 mg/day orally), magnesium (1.5 g/day orally), diazepam (20 mg/day), and quetiapine (50 mg/day), ataxic and oculomotor symptoms fully reversed. However, despite this improvement no change was observed in higher mental functioning.

As a result, when the patient was transferred to our clinic, he was totally disoriented with regard to time, place and persons, was irritable and aggressive; he also had visual and auditory hallucinations, misidentified people, and had severe anterograde and retrograde amnesia and confabulations. Neuropsychological assessment (Clock drawing, Multilingual Aphasia Examination, and a battery of frontal lobe tests) showed a severe impairment in all areas of higher mental functions. Mini Mental State Examination (MMSE) score was 10/30. Blood and biochemistry analysis showed macrocytosis, low folate levels and moderately increased liver enzymes,

findings compatible with chronic alcohol abuse. Ultrasound showed an alcohol-induced fatty liver. The EEG showed diffuse δ and θ activity and brain magnetic resonance imaging (MRI) with contrast showed multiple diffuse lesions in the periventricular region and subcortical white matter compatible with small vessels angiopathy. Moderate cortical atrophy and enlargement of the ventricular system was also evident. A mild sensorimotor axonal polyneuropathy was detected electroneurographically.

Although the protracted WK symptoms made the patient's improvement unlikely, aggressive treatment with thiamine (600 mg/day orally and 300 mg/day *i.m.*) was initiated without changing the previous regimen. Within 3 weeks, the patient's hallucinations and behavioral disturbances fully remitted and tranquilizers were stopped. Meanwhile, cognitive deficits steadily improved and within the next month the patient was fully oriented, did not confabulate and only a circumscribed amnesia for the period of his mental deterioration was present. At the time, his MMSE score was 29/30 and scores on all neuropsychological tests had substantially improved. The patient was discharged and resumed his normal life and work. At his regular follow-up visits, twelve months now after disease onset, he abstains from alcohol and is functioning perfectly well.

Discussion

This case report illustrates the limited knowledge among the medical profession and the misinformation concerning prevention and treatment of WKS, suggesting at the same time some new options concerning the dosage and duration of thiamine supplementation. More precisely, despite existing guidelines there is no general consensus regarding treatment of WE, probably because of a lack of systematic studies on this important issue. Expert opinion suggests intravenous or *i.m.* thiamine replacement treatment at the dosage of 250 mg/day for several days until clinical improvement ceases and thereafter *per os* continuation of thiamine supplementation for several months at a dose of 30 mg twice daily (2, 5-6). British guidelines, in particular, state that for treatment of WE the dose should be 500-700 mg *i.m.*, 8 hourly initially, and continuation with 250 mg/day (5). However, the present report shows that prolonged thiamine administration of high doses (>500-600 mg/day) should be considered in cases with persisting symptoms. In our case, opthalmoplegia and ataxia promptly remitted following initial vitamin supplementation, whereas confusion and cognitive deficits of WKS persisted longer than two months. Apparently, partial treatment allowed the patient to remain in an intermediate stage of WK syndrome, allowing eventual recovery after more aggressive treatment. On the other hand, we cannot rule out a tardive spontaneous recovery even though inappropriately treated WKS is generally considered to be irreversible. This widely held belief has been challenged by the findings of Victor *et al.* in whose series approximately 25% of cases made a complete recovery (3) and lately by Carota *et al.* who described a dramatic recovery associated with the onset of thiamine treatment after the diagnosis was missed for several months (4).

Thiamine requirement for healthy individuals varies between 1-2 mg per day. This requirement increases with chronic alcohol misuse because by damaging the duodenal mucosa ethanol may reduce thiamine absorption up to 90%. Considering that thiamine reserves in the nervous system suffice for 2-3 weeks, thiamine depletion can occur rather quickly. This affects neuronal, glial and endothelial cells through several complex neurotoxic mechanisms which are further determined by interindividual differences in the susceptibility for the development of WKS. Parenteral thiamine replacement is the treatment of choice for WE in the acute phase to ensure adequate absorption. Parenteral thiamine administration rapidly increases thiamine levels in the central nervous system *via* active uptake and additional passive diffusion across the blood-brain barrier (1-2, 5-7).

The multiple mechanisms of neurotoxicity of thiamine deficiency are not yet fully understood; moreover, interindividual differences in WKS vulnerability as well as several other contributing factors, may be at play and determine the precipitation, course and prognosis of the disorder (1-2, 5-7). For instance, in the present case, severe undernourishment and persistent vomiting might have acted synergistically with binge drinking prior to hospital admission resulting in depletion of thiamine reserves. Whatever the case, prolongation of undertreatment of WKS typically precludes significant improvement of symptoms due to irreversible damage in thalamic regions of the brain. Even timely intervention with the usually recommended thiamine doses may fail to reverse the condition. As mentioned above, the outcome of WKS is considered to be poor and therefore, at least whenever WK symptoms persist, higher thiamine doses (over 500 mg/day) for a longer period (at least three months) should be tried. This tactic, however, needs to be more systematically investigated, also taking into account the unavailability of suitable thiamine preparations in several countries, which further complicates the situation.

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