

The background of the entire page is a dense field of golden beer bubbles, creating a textured, shimmering effect. A white rectangular area is positioned on the left side, partially overlapping the bubbles, and a yellow rectangular area is positioned on the right side, also overlapping the bubbles.

# **EARLY DETECTION**

**of Mental and Motor Symptoms  
in the Wernicke-Korsakoff Syndrome**

**JAN WIJNIA**

ERASMUS UNIVERSITEIT ROTTERDAM, 2015



# **Early Detection of Mental and Motor Symptoms In the Wernicke-Korsakoff Syndrome**

**Jan Watze Wijnia**

The clinical signs of Wernicke encephalopathy most often occur within hours to days before a subsequent hospital admission. Wernicke encephalopathy may be identified by the presence of a delirium in malnourished alcoholic patients who have trouble walking. In these patients the delirium is usually due to vitamin B<sub>1</sub> deficiency among other causes, which may be erroneously diagnosed as alcohol withdrawal delirium. In Wernicke delirium the possible loss-of-function mechanisms are proposed to come from microglial activation in the brain.

Other heralding symptoms of vitamin B<sub>1</sub> deficiency are the serious infections that are likely to occur. Wernicke-Korsakoff patients who suffered from an infection during the acute phase are at risk of worse neuropsychological outcomes on follow-up. Assessing the final Korsakoff syndrome diagnosis becomes relevant when the patient with suspected Korsakoff syndrome can walk independently again. In an attempt to further understand the overall symptom profile, we proposed a neuropathological correlate for Korsakoff syndrome involving cerebellar neurocognition at brainstem level. The time course of mental symptoms and gait- and balance disturbances is described in more detail.

Muscle weakness in chronic alcoholism may be related to interdependent deficiencies of vitamin D, phosphate, and magnesium. Further research is needed to determine if vitamin D supplementation can improve muscle function in chronic alcoholic myopathy.

Early Detection of Mental and Motor Symptoms  
In the Wernicke-Korsakoff Syndrome

Vroegsignalering van mentale en motore verschijnselen  
bij het syndroom van Wernicke-Korsakov

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“Wêr no op ta?” sei de drankman doe’t er fallen wie (Fries)  
Waar nu naartoe, zei de alcoholist toen hij gevallen was



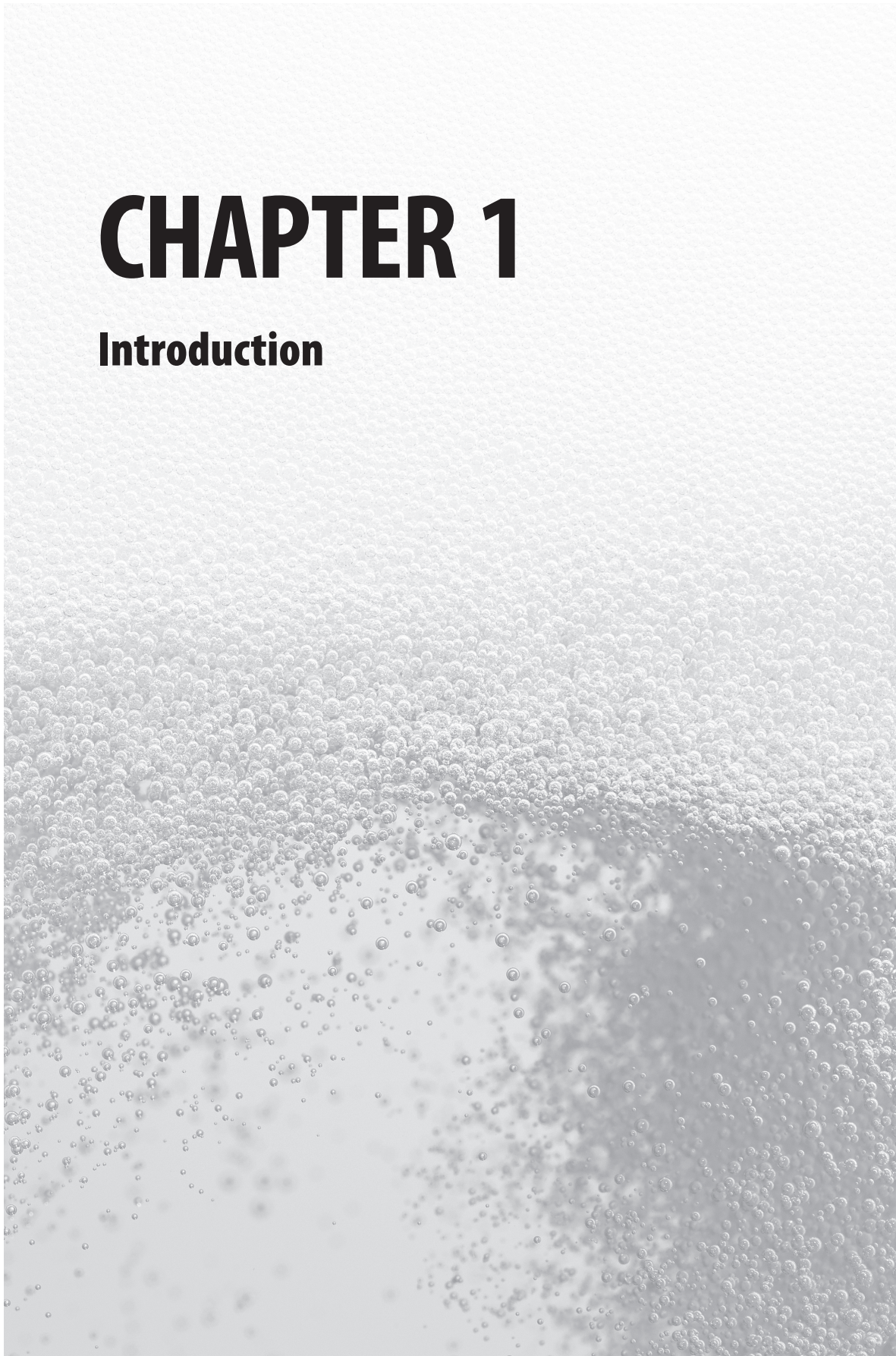
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# CHAPTER 1

## Introduction





The Slingsdael Korsakoff Center in Rotterdam, the Netherlands, is a long-term care facility for patients with Korsakoff syndrome. Many of our patients are referred to us by general and psychiatric hospitals in the Rotterdam region. The Korsakoff Center offers day care, observation and diagnosis, and specialized nursing home care. Slingsdael cooperates with other care facilities supporting similarly affected patients.

## 1.1. BACKGROUND

### 1.1.1. Wernicke-Korsakoff syndrome

Wernicke encephalopathy (WE) and Korsakoff syndrome are considered to be different stages of the same disorder following vitamin B<sub>1</sub> (is thiamine) deficiency, which is called Wernicke-Korsakoff syndrome (WKS). There are excellent monographies on alcohol-related Wernicke-Korsakoff syndrome by Arts (2007) and multidisciplinary guidelines on alcohol-related disorders by Thomson et al (2002) and by van den Brink and Jansen (2009). Yet, it remains to be seen how well we are doing in the diagnosis and management of alcohol-related Wernicke-Korsakoff's (Isenberg-Grzeda et al, 2014). Many cases of Wernicke encephalopathy are missed, despite existing literature and clinical knowledge. This is in agreement with literature from the US and UK: "Over a century after the initial descriptions, Wernicke-Korsakoff syndrome remains diagnostically difficult. [...]. Indeed, even in countries where national guidelines exist, thiamine is still underdosed" (Isenberg-Grzeda et al, 2012).<sup>1</sup>

### 1.1.2. General information

Wernicke encephalopathy is due to thiamine deficiency and is characterized 'classically' by clouding of consciousness,<sup>2</sup> ocular signs,<sup>3</sup> and ataxia (Cook et al, 1998). As Wernicke encephalopathy is essentially a clinical diagnosis warranting prompt treatment, presumptive treatment should not be delayed pending the results of diagnostic procedures.<sup>4</sup> Moreover, serum thiamine levels may be a poor measure of thiamine status (Davies et al, 2011) and results of brain magnetic resonance imaging (MRI) may be found to be normal in some cases of Wernicke encephalopathy (Manzo et al, 2014). If high-dose parenteral thiamine is not given urgently, the biochemical abnormalities that thiamine deficiency causes can lead to irreversible brain damage (Cook et al, 1998). Brain lesions in Wernicke encephalopathy are commonly found in the thalamus, mammillary bodies, subependymal structures (along the third and fourth ventricles and the

1 Quotation marks (" ") are used to enclose words that are quoted from the original source.

2 Acute confusion/ delirium.

3 Nystagmus, ophthalmoplegia.

4 [www.bestpractice.bmj.com/best-practice/monograph/405/diagnosis/step-by-step.html](http://www.bestpractice.bmj.com/best-practice/monograph/405/diagnosis/step-by-step.html)

aqueduct), and the inferior olivary nuclei (Torvik, 1985). 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 (Cook et al, 1998). In postmortem studies, Wernicke encephalopathy occurred in chronic alcoholics at a frequency of 12.5% (Torvik et al, 1982) and in the population as a whole, the figure is ~ 1.5%. However, Wernicke encephalopathy is widely underdiagnosed and so these figures are likely to represent an underestimate of the true prevalence (Cook et al, 1998). The work of Harper et al (1986) demonstrated that the diagnosis of Wernicke encephalopathy was only made clinically in 16% of cases prior to autopsy. In a further review of pathological 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, pre-coma, and coma (Harper et al, 1986).

### **1.1.3. Before admission to Slingsdael Korsakoff Center**

We visited patients in preparation for transferring them to Slingsdael Korsakoff Center. These hospital visits enable us to develop a better understanding of the patients' initial circumstances and the course of Wernicke-Korsakoff syndrome. As we describe in Chapter 2, the managing of alcohol-related disorders includes a hazard of undertreatment, even in patients already admitted to the hospital. Besides standard diagnostic and therapeutic procedures, whenever patients showing behavioral problems are admitted, circumstances of suboptimal medical care may occur, because the managing of these patients generally is no common practice for the admitting team.

The following brief case history is given to further introduce the topic of this thesis on 'Early detection of mental and motor symptoms in the Wernicke-Korsakoff syndrome'.

### **1.1.4. Case history**

A 55-year-old woman was referred to our Korsakoff Center under strong suspicion of having Wernicke-Korsakoff syndrome and alcohol withdrawal delirium. Treatment consisted of intramuscularly thiamine 100 mg/day and clorazepate.

She expressed feelings of anxiety. Presenting symptoms had remained unchanged during the hospital admission. Alcohol abuse existed ever since her youth. The last months she had been secluding herself from her environment.

We examined the patient being in a constant state of anxiety and confusion. She was barefoot, wearing a nightgown. She was unable to walk. There was impairment of her consciousness with fluctuating drowsiness. Orientation of time and space was lost: she thought that she was in a train station, rather than in a hospital. Abnormalities of language included incoherent speech and dysarthria. She thought that she had been

caught by the police, attending nurses would be offending her, and danger was constantly lurking round the corner. Furthermore, there were visual hallucinations.

The symptoms described, represented a delirium. On reexamination four months later signs had changed to a chronic Korsakoff syndrome with apathy, severe memory deficits, and confabulations.

## 1.2. RESEARCH QUESTIONS

### 1.2.1. Main questions

To clarify prevalence rates of delirium in the initial phase of Wernicke-Korsakoff syndrome in our Center, we systematically looked for reports on delirium that preceded the Korsakoff syndrome in our patient group. We sought to find support for the hypothesis that delirium in itself can be a primary presenting feature of Wernicke-Korsakoff syndrome and might be one of the key symptoms of an active Wernicke encephalopathy. Therefore, one of the main questions was:

(I) Are Wernicke encephalopathy and delirium synonymous conditions in malnourished alcoholic patients (Chapter 3 & 5)?

Furthermore, patients suffering from delirium of any cause may show impairments of gait during their delirium episode – however, in the literature no specific information is available on this particular topic (Cf., Axer et al, 2010; Godfrey et al, 2009). As disease-related mobility disturbances are obvious in many clinical cases of Wernicke encephalopathy, we were especially interested in the motor symptoms in combination with the mental changes of the Wernicke-Korsakoff syndrome. Therefore, the second main research question was:

(II) Wernicke-Korsakoff syndrome is a ‘spectrum of disease’ resulting from thiamine deficiency, but would it be possible to more specifically determine its temporal progression regarding the patients’ mobility and mental symptoms (Chapter 4)?

### 1.2.2. Subsidiary questions

When searching for information on Wernicke encephalopathy, our attention was caught by studies, which focused on prisoners on hunger strike ([www.evertdorhoutmees.nl/hongerstaking.html](http://www.evertdorhoutmees.nl/hongerstaking.html), 2005). In the hunger strikes, the prisoners who died, died of Wernicke encephalopathy. Moreover, infections were pointed out as one of the most frequent triggers of death in these cases of Wernicke encephalopathy. Having an infection can increase the utilization of thiamine and may precipitate Wernicke encephalopathy in pa-

tients with marginal thiamine reserves (Donnino et al, 2007; World Health Organization, 1999). Although many studies described the transition of Wernicke encephalopathy to Korsakoff syndrome, the possible role of systemic infections in this transition is not clear.

In our group of end-stage Korsakoff patients, we subsequently made an inventory of the occurrence of infections during the acute Wernicke phase and investigated the effects of these initial infections on the ultimate cognitive outcomes of the Korsakoff syndrome. The research questions here were (Chapter 6):

(III) How common were infections in the initial phase of Wernicke-Korsakoff syndrome in our patient group?

(IV) Were infection parameters related to the cognitive outcomes?

### **1.2.3. Subsidiary questions regarding the patients' impaired mobility**

Muscular weakness and wasting are frequent symptoms of alcoholic myopathy, causing difficulties, e.g., in rising from a chair or in climbing a staircase. In chronic alcoholic myopathy, improvement of muscle weakness usually takes at least 2–3 months (Diamond & Messing, 1994) up to 6–9 months following alcohol abstinence (Preedy & Peters, 1994; Slavin et al, 1983).

Vitamin D deficiency is a well-recognized cause of myopathy and excessive drinking is often associated with low or subnormal levels of vitamin D. As many alcoholic patients have low vitamin D levels, this prompted us to raise the question whether the muscle weakness might be caused by vitamin D deficiency.

This research question was formulated as follows (Chapter 7 & 8):

(V) Is vitamin D deficiency a confounder in alcoholic muscle weakness?

## **1.3. SUPPLEMENTARY CHAPTERS**

The relation of sign-symptoms and neuropathological substrate of delirium or WKS is largely unknown. Therefore future challenges may be found in uniting the spectrum of WKS symptoms in terms of successive neuropathological changes, including the acute delirium and the end-stage symptoms. In an attempt to further understand the WKS symptom profile, we proposed a neuropathological correlate for Korsakoff syndrome involving cerebellar neurocognition at brainstem level (Chapter 9).

Finally, we gave some background information (Chapter 10) on thiamine treatment of Wernicke encephalopathy according to recommendations of current guidelines.

The subject of delirium due to thiamine deficiency and impaired mobility is further introduced in the following Chapter 2.<sup>5</sup>

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5 The results of this thesis are presented in Chapters corresponding with papers published in, or submitted to, medical journals.

Some modest editing was done for section layout (paragraph numbers, e.g., 1.1.1.), Figure/ Table numbers (e.g., Figure 1–1), uniform spelling, and frequently used words or descriptions: ‘behavior’, ‘esophageal’, ‘summarized’, ‘abuse’, ‘alcoholic patient’, ‘Wernicke encephalopathy’, ‘Korsakoff syndrome’, ‘elderly care physician’, ‘our Center’, rather than: ‘behaviour’, ‘oesophageal’, ‘summarised’, ‘misuse’, ‘alcoholic’, ‘Wernicke’s encephalopathy’, ‘Korsakoff’s syndrome’, ‘physician–elderly care’, or repeatedly ‘Slingedael Korsakoff Center’.

References to Chapters in the main body of the text correspond to the full citations used in the papers, e.g., ‘(Chapter 3)’ for citation rather than ‘(Wijnia et al, 2012)’.



# CHAPTER 2

## Difficulties in identifying Wernicke delirium

Wijnia JW, Nieuwenhuis KG

European Journal of Internal Medicine 2011; 22(6):e160–161

Letter to the Editor

Keywords: Delirium, Alcoholism, Thiamine

**ABSTRACT**

In daily practice, we saw disappointing results with respect to the number of patients that have been appropriately treated with parenteral thiamine after admission to general or psychiatric hospitals. Delirium and inability to walk are important symptoms of Wernicke encephalopathy, but can easily be mistaken for alcohol withdrawal delirium. Apparently, a history of alcohol abuse may unintentionally influence the diagnosis of patients with delirium, such that Wernicke encephalopathy is overlooked. In order to identify possible Wernicke encephalopathy in malnourished alcoholic patients, it is essential to give proper attention to any signs of delirium and to problems with gait and posture, as well.

## 2.1. INTRODUCTION

Wernicke-Korsakoff syndrome is one of the serious consequences of vitamin B<sub>1</sub> deficiency, in affluent countries most commonly seen in chronic alcoholism. Wernicke encephalopathy is an acute, potentially life-threatening condition that may initially be reversible, if treated adequately by giving intravenous thiamine (Arts, 2007; Thomson et al, 2002; van den Brink & Jansen, 2009).

Slingedael Korsakoff Center offers a long-stay facility for patients with Korsakoff syndrome. For triage purposes, we visited referred patients previous to admission. Most of the patients were post-discharge patients of general or psychiatric hospitals and treated by specialists in psychiatry, neurology or internal medicine. In daily practice we found that several of these patients appear to not be getting appropriate thiamine treatment according to multidisciplinary guidelines for managing suspected Wernicke encephalopathy (Thomson et al, 2002; van den Brink & Jansen, 2009).

## 2.2. HOSPITAL ADMISSION

The reason why an alcoholic patient is hospitalized, can be gradually increasing physical illness, but is often a collapse. Depending on the present symptoms this may lead to admission to various departments: Internal Medicine, Geriatrics, Pulmonology, Cardiology, Neurology, Psychiatry, Surgery, Urology, or ENT-department.<sup>6</sup> On our hospital visits, members of the admitting team often expressed feelings that the confused alcoholic patient 'had fallen between two stools' – currently having been referred to a department that would not be the appropriate one. The patients had not been eating well for at least several weeks before admission and appeared seriously confused on admission. They indeed suffered from a long history of alcohol abuse, but the onset of Wernicke-Korsakoff syndrome was often associated with one of the first clinical admissions. This finding emphasized the need for an active treatment approach in malnourished alcoholic patients once they are admitted to the hospital. Undertreatment may occur because of a missed diagnosis.

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6 ENT, Ear, Nose & Throat-department, e.g., admitting a confused alcoholic patient with head and neck cancer.

### 2.3. CLASSIFICATION OF DELIRIUM

According to literature and our experience, Wernicke encephalopathy is often undiagnosed in its less evident presentations (Arts, 2007; Thomson et al, 2002; van den Brink & Jansen, 2009). In the initial stage, different *syndromes* with confusion, such as delirium and Wernicke-Korsakoff's, are difficult to distinguish in relation to the underlying disorder, e.g., alcohol withdrawal or thiamine deficiency. In the literature this is described mainly from the point of view that patients with delirium tremens may often also have Wernicke encephalopathy (Thomson et al, 2002; McKeon et al, 2008).

Knowing the classification of the delirium in patients with alcohol abuse histories should not make a major difference in clinical management or outcome of thiamine treatment, because any patient with heavy alcohol consumption before hospitalization should be routinely given thiamine treatment regardless of presence or absence of delirium. However, in current practice of about seventeen referring hospitals, we found that deliria without obvious physical cause had frequently been indicated as 'alcohol withdrawal' delirium, even though it was not made clear whether or not the patient had stopped or diminished drinking alcohol. Apparently, a history of alcohol abuse influences the diagnosis of patients with delirium, such that a potentially underlying cause for delirium, such as Wernicke encephalopathy, may be overlooked (Rosenbaum, 2003). In several cases this represented considerable diagnostic error, leading to inadequate treatment with thiamine given nonparenterally, in too small a dose, or too late (Thomson et al, 2002).

### 2.4. IMPAIRED GAIT

In order to identify possible Wernicke encephalopathy, it is essential to give proper attention to any problems with gait and posture. Although the formal examination of cerebellar signs, including ataxia may be difficult in more severely ill patients, it is obvious that the patient cannot walk normally. Patients may have been found on the ground after different periods of time, ranging from minutes to even days following a fall, and are now bedridden or wheelchair-bound. The differential diagnosis of gait disorders in alcoholic patients is extensive: alcohol intoxication, alcoholic polyneuropathy, alcoholic myopathy, rhabdomyolysis, central pontine myelinolysis, subdural hematoma, cerebellar atrophy. Despite this fact, impaired gait is an important feature of Wernicke encephalopathy.

## 2.5. DELIRIUM AND WERNICKE ENCEPHALOPATHY

As Wernicke himself described: “The question of whether the signs of alcoholic delirium should be regarded as a complication or as a separate general manifestation pertaining to this (Wernicke’s) disease may be posed but cannot be decided” (Thomson et al, 2008a). During our visits we frequently saw patients who were wheelchair-bound, suffering from a delirium, and in several cases we observed that the delirium had been assigned to alcohol withdrawal, even if no alcohol withdrawal was found. We had to conclude that the delirium might have been a possible expression of Wernicke encephalopathy, as was illustrated by the course of symptoms in patients showing an acute onset of delirium subsequently progressing into a chronic Korsakoff syndrome.

To summarize: In self-neglecting alcoholic patients, delirium can be an expression of Wernicke encephalopathy and this should be treated as such to prevent further damage from the neurological complications of thiamine deficiency. We hope this approach will contribute to changing the discharge diagnosis of delirium: from ‘alcohol withdrawal delirium’ to ‘treated Wernicke encephalopathy’.



# CHAPTER 3

## **Evolution of Wernicke-Korsakoff syndrome in self-neglecting alcoholics: preliminary results of relation with Wernicke delirium and diabetes mellitus**

Wijnia JW, van de Wetering BJ, Zwart E, Nieuwenhuis KG, Goossensen MA

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Regular article

Keywords: Alcohol, Medical complications, Psychiatric aspects, Withdrawal, Assessment

**ABSTRACT**

We present a descriptive, retrospective study of initial symptoms, comorbidity, and alcohol withdrawal in 73 alcoholic patients with subsequent Korsakoff syndrome. In 25/73 (34%) of the patients the classic triad of Wernicke encephalopathy with ocular symptoms, ataxia, and confusion, was found. In at least 6/35 (17%) of the initial deliria (95%-confidence interval: 10–25%) we observed no other underlying causes, thus excluding other somatic causes, medication, (recent) alcohol withdrawal, or intoxication. We suggest that these deliria may have been representing Wernicke encephalopathy. A high frequency (15%) of diabetics may reflect a contributing factor of diabetes mellitus in the evolution of the Wernicke-Korsakoff syndrome.

### 3.1. INTRODUCTION

#### 3.1.1. Clinical features

The Korsakoff syndrome is a chronic condition that may emerge when the acute phase of the Wernicke-Korsakoff syndrome resolves (American Psychiatric Association, 2000; Thomson et al, 2002). Korsakoff syndrome is characterized by impairments of memory and executive functions (Table 3–1), whereas the patients themselves experience no problems due to reduced awareness of illness. Disturbances of executive functioning constitute an important component of severe functional limitations that can be observed in Korsakoff patients, regarding initiative, planning, organizing and regulating of behavior (Goossensen et al, 2007; Kessels et al, 2008; Thomson et al, 2002).

Timely and adequate treatment of thiamine deficits in patients with Wernicke-Korsakoff syndrome is critical to prevent the progress into the end-stage of the disease (Thomson et al, 2002). When the Korsakoff syndrome is diagnosed without clinical

**Table 3–1.** Definitions

<b>Korsakoff syndrome</b>	<p>The diagnostic criteria of alcohol-induced persisting amnesic disorder are contained in the DSM-IV category of substance-induced persisting amnesic disorder:</p> <ul style="list-style-type: none"> <li>A. The development of memory impairment as manifested by impairment in the ability to learn new information or the inability to recall previously learned information.</li> <li>B. The memory disturbance causes significant impairment in social or occupational functioning and represents a significant decline from a previous level of functioning.</li> <li>C. The memory disturbance does not occur exclusively during the course of a delirium or a dementia and persists beyond the usual duration of alcohol intoxication or withdrawal.</li> <li>D. There is evidence from the history, physical examination, or laboratory findings that the memory disturbance is etiologically related to the persisting effects of alcohol use.<sup>1</sup></li> </ul> <p>Clinical description: “Sergei Korsakoff characterized the memory disorder as occurring in a setting of clear consciousness, such that the patient gave the impression in conversation that he was entirely in possession of his faculties but showed a severe impairment current and recently memory, asking the same questions over and over again, reading the same page for hours on end, and not being able to recognize people whom he had met many times since the onset of the illness. Current en recent memory was affected more than remote memory, but the impairment could involve memories from up to 30 years earlier. Sometimes, the disorder was associated with patients inventing ‘fictions’ (confabulations) in their discourse, and these false recollections often represented real memories jumbled up and recalled out of temporal sequence.”<sup>2</sup></p>
<b>Wernicke encephalopathy</b>	The classic triad of ocular motility abnormalities: external ophthalmoplegia and/ or nystagmus, ataxia affecting primarily the gait, and mental confusion or delirium. <sup>2,3</sup>
<b>Alcohol withdrawal delirium</b>	Delirium after cessation or reduction of previously significant and/ or prolonged alcohol abuse. The worst symptoms occur the 2 <sup>nd</sup> –5 <sup>th</sup> day following abstinence. <sup>4</sup>

<sup>1</sup> American Psychiatric Association, 2000. <sup>2</sup> Kopelman et al, 2009. <sup>3</sup> McKeon et al, 2008. <sup>4</sup> van den Brink & Jansen, 2009.

features of preceding Wernicke encephalopathy (the triad of ocular symptoms, gait disorder, and confusion), the syndrome may have developed insidiously. However, the presence of Wernicke encephalopathy is often not recognized because of an atypical or incomplete presentation (Thomson et al, 2002; Thomson & Marshall, 2006a; van den Brink & Jansen, 2009). An early assessment of the risk of Wernicke-Korsakoff syndrome is essential to prevent further damage from the neurological complications of thiamine deficiency.

### **3.1.2. Initial delirium**

Slingedael Korsakoff Center offers a long-stay facility for patients with Korsakoff syndrome. For triage purposes, an elderly care physician and psychologist visited all referred patients before admission. During these visits we frequently saw patients who were wheelchair-bound and suffering from delirium. In several cases we observed that the delirium had been assigned to alcohol withdrawal, even though it was not made clear whether or not the patient had recently stopped or diminished drinking alcohol. Because of these ‘anecdotal’ observations we wondered whether the delirium might have been a primary manifestation of encephalopathy prior to the development of Korsakoff syndrome, on the basis of an unrecognized Wernicke encephalopathy with incomplete presentation.

### **3.1.3. Wernicke’s syndrome**

The concept of a classic triad of signs and symptoms in Wernicke encephalopathy was based on the original description by Carl Wernicke. The triad consists of an acute onset of a confusional state and impairment of consciousness, ataxia, and eye signs (nystagmus and ophthalmoplegia). However, as Wernicke himself described, and has been shown in subsequent studies, other important clinical signs and symptoms, such as nausea, vomiting, loss of appetite and emotional changes, are often present before the later ‘classical’ signs appear (Thomson et al, 2008a; 2008b). Furthermore, Wernicke wrote: “The question of whether the signs of delirium potatorum should be regarded as a complication or as a separate general manifestation pertaining to this (Wernicke’s) disease may be posed but cannot be decided” (Translation by Thomson et al, 2008a).

In a review of clinical findings in alcoholic and non-alcoholic patients whose diagnosis of Wernicke-Korsakoff syndrome has been confirmed postmortem, the symptoms selected for recording were dependent upon what clinicians considered to be the diagnosis at the time. Delirious symptoms were reported to be present in four out of 13 studies, but unfortunately not as prevalence rates per study (Thomson et al, 2008b).

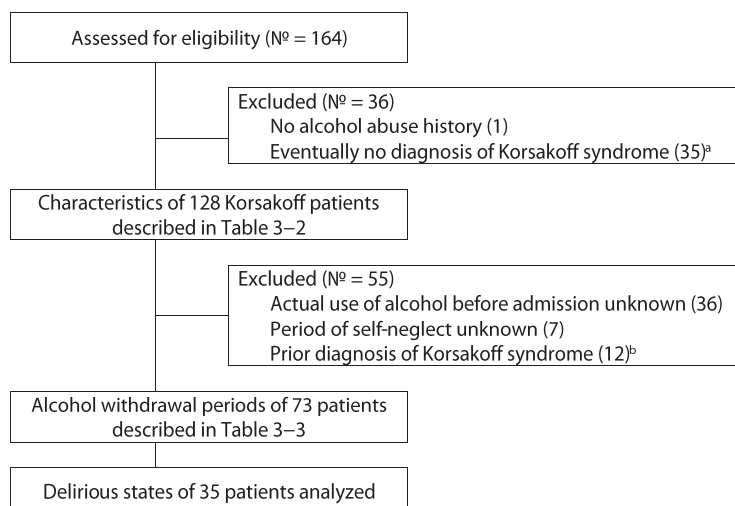
### 3.1.4. Aim of the study

We systematically examined the symptoms that preceded the Korsakoff syndrome in our patient group. We explored the idea that delirium in itself can be a primary presenting feature of Wernicke-Korsakoff syndrome and might be one of the key symptoms of an active Wernicke encephalopathy.

## 3.2. METHOD

### 3.2.1. Data collection

We registered all applications for admission to Slingsdael Korsakoff Center from April 1, 2005 to March 31, 2010. The patients' medical history was obtained from information on application forms, discharge letters, records of general practitioners, and other sources, such as a parent or a spouse. Following diagnostic hospitalization in a general or psychiatric hospital, or alcohol clinic, patients may have been admitted first to a nursing home elsewhere or discharged home, before being referred to the Korsakoff department of our nursing home. In this paper, the prior (clinical) admission in which Korsakoff syndrome was diagnosed or strongly suspected, will be denoted as 'diagnostic admission'. Patients were visited within 1–2 weeks after application for admission to our Center. Data collection involved the patients' age, sex, age of onset and duration of alcohol abuse, information on alcohol consumption and self-neglect (malnutrition)



**Figure 3–1.** Phases of data sampling in patients referred to Slingsdael Korsakoff Center

N°, number of patients. <sup>a</sup> Dementia (17), acquired brain injury (8), hepatic encephalopathy (2), minimal or atypical cognitive symptoms (6), other (2). <sup>b</sup> Long-standing diagnosis having been established before the current illness episode.

before the diagnostic admission, number of previous admissions up to and including the diagnostic admission, and the name of institution signing up for admission to our Center. Reasons for exclusion of the patients from the study are given in Figure 3–1.

### **3.2.2. Initial symptoms**

Symptoms preceding the Korsakoff syndrome were identified on the basis of registration data, the patients' medical history obtained from other sources, and personal observation. This included data of the diagnostic admission concerning the state of consciousness, (dis)orientation, memory disorders, executive (dys)functioning, confabulations, presence of a delirium, presence of the classic triad of Wernicke encephalopathy, or collapse (patient had been found on the floor). We also registered data of current and previous psychiatric/ somatic comorbidity, and the social situation of the patient.

### **3.2.3. Assessment of alcohol use**

For the aim of the research, possible alcohol withdrawal at the time of the diagnostic admission was assessed based on various sources: data of emergency departments or clinical departments regarding signs of alcohol intoxication; if available test results on blood alcohol concentrations; data on alcohol consumption for the last days/ weeks before admission, previous GP consults; and/ or outpatient care. Because presenting symptoms of alcohol withdrawal delirium may be considered most severe during the 2<sup>nd</sup>–5<sup>th</sup> day of alcohol withdrawal (van den Brink & Jansen, 2009), we defined alcohol withdrawal delirium unlikely to happen in patients that were abstinent for more than one week. And by definition, we would not expect alcohol withdrawal delirium on admission if patients had continued drinking. Therefore we chose to divide previous alcohol abuse into three groups: (i) The patient continued drinking up until the diagnostic admission, (ii) the patient had discontinued or diminished alcohol drinking during the week before admission, and (iii) the patient had discontinued drinking alcohol for more than one week before admission.

### **3.2.4. Korsakoff diagnosis**

The diagnosis of Korsakoff syndrome can usually appropriately be made after a four week (van den Brink & Jansen, 2009) to six week period (Goossensen et al, 2007) of alcohol abstinence. Patients were alcohol abstinent during the diagnostic admission and were not allowed to drink alcohol in our Center. The diagnosis of Korsakoff syndrome was made by clinical assessment of consulting specialists in psychiatry or neurology, and (infrequently) by neuropsychological assessment during the previous hospitalization period. If patients were admitted to our Center, additional tests were done after 2–6 months to assess the Korsakoff syndrome. Neurocognitive assessment demonstrating a relatively isolated amnestic disorder (American Psychiatric Association,

2000) with a relatively intact intellect, and executive dysfunctioning, were documented by neurocognitive assessment, including: Cambridge Cognitive Examination (CAMCOG), Kaufman Short Neurological Procedure, Rivermead Behavioral Memory Test, 15 Words Test, Visual Association Test, Groningen's Intelligence Test (an alternative for Wechsler Adult Intelligence Scale), Verbal Fluency Test, Figure Fluency Test, Clock Drawing Test, Behavioral Assessment of the Dysexecutive Syndrome (BADS), Stroop Color-Word Test, Trail Making Test part A & B, and Numerical Series Test.

### 3.3. RESULTS

#### 3.3.1. Patient characteristics

Patient data of the 128 Korsakoff patients are listed in Table 3–2. Of these patients, 122 (95%) were single and living alone, 19 of them were divorced, 8 widow(er), and another 8 homeless. In 69% of patients and number of admissions known, the diagnosis of Wernicke-Korsakoff syndrome was made at the first admittance following a prolonged period of heavy alcohol abuse and serious self-neglect. Patients may have been staying in hospital for 2–8 weeks before they were visited. Of the 128 patients with a Korsakoff diagnosis, eventually 11 patients were not admitted to our Center, but admitted elsewhere. In seven of these patients the diagnosis was made by clinical assessment of consulting specialists in psychiatry or neurology, without further neurocognitive assessment.

#### 3.3.2. Alcohol withdrawal

Additional data on the duration of alcohol withdrawal were available in a smaller group of 73/128 Korsakoff patients (Table 3–3). These patients were diagnosed having a delirium in 35/73 (48%) and the triad symptoms of Wernicke encephalopathy in 25/73 (34%). The patients had multiple potential causes for delirium, including alcohol withdrawal, alcohol intoxication, hepatic disease, delirium associated with pneumonia, and delirium associated with cerebrovascular disease.

In 15/35 (43%) of the deliria we had to conclude that there was no alcohol withdrawal involved as a contributing factor. That is, 12/35 (34%) of the delirious patients were already delirious on admission, but had not yet stopped or diminished alcohol drinking, and 3/35 (8.5%) were delirious after an abstinence period for more than one week. A concomitant diagnosis of Wernicke encephalopathy was made in 8/15 (53%) of these patients, according to classic symptoms having been observed of ocular symptoms, gait disorder and confusion. In the other 7/15 patients with delirium, in six patients no other possible causes were identified. None of those six patients received medication before the index hospitalizations, which theoretically could also have contributed to

**Table 3–2.** Korsakoff patients referred to Slingsdael Korsakoff Center, Rotterdam

Characteristics		Mean (range)	Patients
Age	Male	58 (33–87) years	105
	Female	62 (41–80) years	23 (18%)
Quantity of pure alcohol <sup>a</sup>	Male	275 (60–800) mL/day <sup>b</sup>	
	Female	230 (120–700) mL/day <sup>b</sup>	
Length of alcohol abuse		31 (2–64) years <sup>c</sup>	
Number of admissions <sup>d</sup>		2.4 (1–10) <sup>e</sup>	
Referred by	General Hospital		39 (30%)
	Alcohol Clinic		21 (16%)
	Psychiatric Hospital		21 (16%)
	Nursing Home		22 (17%)
	General Practitioner		20 (16%)
	Other		5 (4%)
Period of self-neglect (malnutrition)	< 1 Month		11 (9%)
	≥ 1 Month, < 1 Year		28 (22%)
	≥ 1 Year		82 (64%)
	Not known		7 (5%)
Increase of self-neglect (not eating at all)	< 3 Weeks		13 (10%)
	≥ 3 Weeks, < 6 Weeks		7 (5.5%)
	≥ 6 Weeks		7 (5.5%)
	No increase mentioned or known		101 (79%)
Presenting symptoms	Delirium		46 (36%)
	Wernicke encephalopathy (triad)		32 (25%)
	Collapse, found on the floor		25 (20%)
Psychiatric disorders	Depression		23 (18%)
	Personality disorder		20 (16%)
	Psychosis/ Hallucinoses		9 (7%)
	Other		9 (7%)
Somatic disorders	Liver cirrhosis/ Alcoholic hepatitis		40 (31%)
	Diabetes mellitus		19 (15%)
	COPD/ Pneumonia		16 (12%)
	Stroke/ Subdural hematoma		15 (11.5%)
	Vascular disease, including myocardial infarction		9 (7%)
	Carcinoma		9 (7%)
	Pancreatitis		7 (5%)
	Peptic ulcers/ Esophageal stenosis		5 (4%)
	Other		9 (7%)

Total N° = 128 patients. <sup>a</sup> Beer 250 mL = 12.5 mL pure alcohol, wine 100 mL = 12 mL pure alcohol, liquor 35 mL = 12.25 mL pure alcohol. <sup>b</sup> In 41 (39%) men, 13 (57%) women; unspecified as 'Alcohol abuse' in the other patients. <sup>c</sup> Unspecified as 'Chronic abuse' in 72 (56%) patients. <sup>d</sup> Before the Korsakoff syndrome was diagnosed. <sup>e</sup> Not known in 26 (20%) patients.

**Table 3–3.** Symptoms preceding Korsakoff syndrome, diagnosed as delirium and/ or Wernicke encephalopathy triad

Nº is 73 patients			Delirium		No diagnosis of delirium is made during admission	
			Present upon admission	Developing during admission		
Alcohol drinking	Nº	WE	Nº	WE	Nº	WE
Continued up till admission	12	6	9	1	22	6
Discontinued or diminished during week before admission	11	3	0	0	5	3
Discontinued for more than a week before admission	3	2	0	0	11	4
Total	26	11	9	1	38	13

Nº, number of patients. WE, number of patients with Wernicke encephalopathy triad symptoms.

the occurrence of delirium; and also in these patients, no alcohol intoxication, nor any other underlying somatic causes could be confirmed. In summary, in 6/35 (17%) of the delirious patients, no recent alcohol abstinence, alcohol intoxication, somatic comorbidity, nor classic Wernicke encephalopathy was observed in relation to the delirium. These findings in a selected patient group of Korsakoff patients signified that at least 17% (95%-CI: 10–25%) of the delirious conditions in the early stages of WKS may have occurred on the basis of an unrecognized Wernicke encephalopathy with incomplete presentation.

### 3.3.3. Diabetes mellitus

A striking finding was the high frequency of diabetics in our patient group (Table 3–2). That is, in 19/128 (15%) of the Korsakoff patients (95%-CI: 8.5–21%) diabetes mellitus was found as a comorbid condition. If corrected for age and sex, we would expect 7% diabetics according to the prevalence of diabetes in the Netherlands (Statistics Netherlands, 2007/ 2008).

### 3.3.4. Missing data

In 36/128 (28%) of the patients no detailed data were available on actual alcohol consumption at the time of presentation. The amount of missing data was negatively associated with the number of admissions prior to the diagnostic admission – previous information being less available and recent information being less detailed, when the patient had experienced more admissions prior to the diagnostic admission.<sup>7</sup>

7 We found a negative association between the patients' total number N (1–10) of hospital admissions and the percentage (72%–0%) of patients with a more detailed medical history regarding their alcohol consumption before the current N<sup>th</sup> admission – other than 'chronic alcoholism' or 'chronic alcohol abuse'.

### 3.4. DISCUSSION

#### 3.4.1. Incomplete Wernicke's

It is already well known that it is common for Wernicke syndrome to present incompletely or partially, with only one or two of the pathognomonic features and that many cases of Korsakoff syndrome occur without a preceding episode of Wernicke encephalopathy (Kopelman et al, 2009; Thomson & Marshall, 2006a). For these reasons, it is established good practice that patients with a history of alcohol and current presentation of delirium receive treatment even without the triad of Wernicke encephalopathy.

#### 3.4.2. Background information

Victor et al (1989, p. 195) concluded: "The diagnosis of Wernicke's disease is made most readily on the basis of the acute appearance of ocular palsies, nystagmus, ataxia of gait, and disturbances of consciousness and mentation, which may present single or in various combinations." More than 80% of the patients show signs of polyneuropathy as well, and associated liver disease is found in two-thirds of the patients (Thomson et al, 2008b). The work of Harper et al (1986) demonstrated that the diagnosis of Wernicke encephalopathy was only made clinically in 16% of cases prior to autopsy.

Thomson et al (2008b) are concerned with the early identification of patients at risk of developing Wernicke encephalopathy and who have developed the prodromal symptoms of thiamine deficiency. They have prepared several guidelines for identifying early thiamine deficiency and to aid the doctor in predicting whether the patient has Wernicke encephalopathy (Thomson et al, 2002; 2008b). Early sign-symptoms of thiamine deficiency are involving loss of appetite, nausea/ vomiting, fatigue, weakness, apathy, giddiness, diplopia, insomnia, anxiety, difficulty in concentration, and/ or loss of memory (Thomson et al, 2008b).

Caine et al (1997, p. 54) developed operational criteria to differentiate between Wernicke encephalopathy alone or in combination with Korsakoff's psychosis or hepatic encephalopathy: "The criteria for Wernicke encephalopathy require two of the following signs: (i) dietary deficiency, (ii) oculomotor abnormalities, (iii) cerebellar dysfunction, and (iv) either altered mental state or mild memory impairment." According to the information in Caine's article, however, six out of the 40 patients (15%) with Wernicke encephalopathy pathology, were not clinically diagnosed using these operational criteria.

#### 3.4.3. Thiamine therapy

Because of atypical presentation, Wernicke encephalopathy is difficult to diagnose (Thomson et al, 2002; van den Brink & Jansen, 2009). Therefore, immediate initiation of thiamine treatment is advised (van den Brink & Jansen, 2009) in every alcoholic patient presenting with self-neglect, cognitive impairment and gait disorders or polyneuropathy.

thy (high risk of Wernicke encephalopathy). In case of significant other symptoms, e.g., acute confusion, decreased conscious level, or eye movement disorders, and thereby suspicion of an existing Wernicke encephalopathy, higher amounts of thiamine are advised; length of treatment is dependent on the clinical course (van den Brink & Jansen, 2009). For a full outline of thiamine therapy, the reader is advised to consult the Free PubMed Central article by Thomson et al (2002), available at [www.ncbi.nlm.nih.gov/pubmed/12414541](http://www.ncbi.nlm.nih.gov/pubmed/12414541).

#### **3.4.4. Mental confusion**

In general, different syndromes with confusion, such as Wernicke-Korsakoff's and delirium, are difficult to distinguish in relation to the underlying disorder, e.g., thiamine deficiency or alcohol withdrawal (Rosenbaum, 2003). In fact, the two conditions – Wernicke encephalopathy and alcohol withdrawal – can co-exist. In the literature this is described mainly from the point of view that patients with delirium tremens may often also have Wernicke encephalopathy (McKeon et al, 2008; Thomson et al, 2002). However, delirium is a possible expression of Wernicke encephalopathy itself as well, given that delirium is one of the features of Wernicke encephalopathy. In our study, this symptom pattern was observed in at least a group of patients without (recent) alcohol withdrawal, showing an acute onset of delirium subsequently progressing into a chronic Korsakoff syndrome. Seventeen per cent of the patients with delirium had no evidence of underlying somatic causes, no (recent) alcohol withdrawal or intoxication, and no triad symptoms of Wernicke encephalopathy. We assumed that these patients with unexplained delirium who went on to develop Korsakoff syndrome may have had some type of incomplete form of Wernicke encephalopathy without the classic symptoms of ophthalmoplegia, nystagmus, and ataxia.

#### **3.4.5. Epidemiological findings**

Our patient group represented a specialized population of patients being referred to Slingsdael Korsakoff Center. The total number of Korsakoff patients in our region, i.e., the city of Rotterdam and its surrounding areas, is unknown. The Rotterdam-Rijnmond Public Health Service (GGD) made an estimation of 275–450 Korsakoff patients (corresponding with a prevalence of 3.0–4.8 patients per 10,000 inhabitants) living at home, in homeless shelters, residential care homes, or staying in alcohol clinics, general/ psychiatric hospitals, and other care facilities, in Rotterdam and surrounding areas (Wierdsma et al, 1994).

#### **3.4.6. Patient characteristics**

We provided data on the initial hospitalization of Korsakoff patients that led to the diagnosis and categorized patients as to whether they had Wernicke encephalopathy,

alcohol withdrawal, or some other type of delirium at the time of presentation. Most of the patients that were referred to our Center, were inpatients of general or psychiatric hospitals, and diagnosed by specialists in psychiatry, neurology or internal medicine. Patients studied had not been eating well for at least several weeks, and appeared seriously confused on admission. The patients had suffered from a long history of alcohol abuse, but the diagnosis of Wernicke-Korsakoff syndrome was often associated with one of the first clinical admissions. This finding emphasized the need for an active treatment approach in self-neglecting alcoholic patients once they are admitted to the hospital.

### **3.4.7. Diabetes mellitus**

It is not clear whether heavy alcohol abuse might have been a contributing factor in the pathogenesis of diabetes (Carlsson et al, 2005; Koppes et al, 2005; van den Brink & Jansen, 2009), or whether diabetic patients may be more sensitive in getting Korsakoff syndrome. As described in the literature, acute alcohol intoxication may be associated with hypoglycemia (van der Meulen, 1976), and occasionally chronic alcohol abuse may be as well (Sporer et al, 1992). Treatment of hypoglycemia (Thomson et al, 2002) or administering of glucose (Corcoran et al, 2002; Muller Kobold & Endtz, 1975) without correction of a coexisting thiamine deficiency in chronic alcoholism holds the risk of precipitating Wernicke encephalopathy.<sup>8</sup> This serious condition, and progression to Korsakoff syndrome, can probably be successfully prevented by administering thiamine prior to glucose (Corcoran et al, 2002) or simultaneously with glucose (Thomson et al, 2002).

### **3.4.8. Limitations**

The application of benzodiazepine medication for prevention of alcohol withdrawal delirium and length of delirium periods were not systematically assessed in this study. There were too few data on thiamine blood levels (18 patients) to be of use for systematic analysis. Although our findings suggest that a delirium may represent the initiation phase of Wernicke-Korsakoff syndrome, extensive confirmation of this pattern requires further research. The completed available patients' information on alcohol withdrawal was small in number, but it will be difficult to obtain reliable data, considering self-neglecting patients seldom seek medical care. Wernicke encephalopathy might also be confused with alcohol intoxication delirium, but the proportion of alcoholic delirium contributed by patients with Wernicke-Korsakoff syndrome is unknown. We did not find any epidemiologic data concerning the incidence of alcohol intoxication delirium.

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8 Administering of glucose, e.g., parenteral feeding, enteral feeding, refeeding, IV glucose following starvation.

### **3.5. CONCLUSION**

In patients with long alcohol abuse histories, a coincidental collapse may have been the reason of admission. These patients often appeared seriously confused on admission. According to our experience, any delirium in malnourished alcoholic patients is representing Wernicke's syndrome – until proven otherwise. The phenomenon of Wernicke delirium does not present a new entity, but might be one of the answers to the original question of Carl Wernicke: whether alcohol-related delirium should be regarded as a complication or as a separate general manifestation pertaining to his eponymous encephalopathy.

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# CHAPTER 4

## **Need for early diagnosis of mental and mobility changes in Wernicke encephalopathy**

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Case report

Keywords: Alcohol-related disorders, Korsakoff syndrome, Wernicke encephalopathy, Delirium, Thiamine

**ABSTRACT**

The intra-individual course of Wernicke-Korsakoff syndrome has not been studied extensively, nor has the temporal progression of gait disturbances and other symptoms of Wernicke encephalopathy. Here we present the detailed history of a patient whose acute symptoms of Wernicke encephalopathy were far from stable. We follow his mobility changes and the shifts in his mental status from global confusion and impaired consciousness to more selective cognitive deficits. His Wernicke encephalopathy was missed and left untreated, being labeled as 'probable' Korsakoff syndrome. Patients with a history of self-neglect and alcohol abuse, at risk of or suffering with Wernicke encephalopathy, should receive immediate and adequate vitamin replacement. Self-neglecting alcoholics who are bedridden may have severe illness and probably active Wernicke encephalopathy. In these patients, mobility changes, delirium, or impaired consciousness can be an expression of Wernicke encephalopathy, and should be treated to prevent further damage from the neurologic complications of thiamine deficiency.

4.1. INTRODUCTION

4.1.1. Wernicke encephalopathy

Wernicke encephalopathy is a neurologic disease caused by vitamin B<sub>1</sub> (thiamine) deficiency (Table 4–1). Most patients with Wernicke encephalopathy have a background of chronic alcoholism and self-neglect (Sechi & Serra, 2007). Patients with Wernicke encephalopathy may present with the classic triad symptoms of ocular motility abnormalities, ataxia primarily affecting gait, and confusion or delirium (Thomson et al, 2002). More often, however, patients show disturbances of attention and consciousness ranging from delirium to profound unconsciousness, in combination with a loss of the ability to walk. Because of this variety in presentation, Wernicke encephalopathy can mimic other conditions such as alcohol withdrawal delirium, or may be mistaken for other conditions that produce cognitive disturbances. Ultimately, patients with Wernicke encephalopathy whose thiamine deficiency continues may develop Korsakoff syndrome, which is characterized by chronic amnesia. Wernicke-Korsakoff syndrome is a combination of the two conditions.

Table 4–1. Defining characteristics

<b>Wernicke encephalopathy</b>	Neurologic disorder caused by lack of vitamin B <sub>1</sub> and most often affecting chronic alcohol abusers. The classic symptom triad is ocular motility abnormalities (external ophthalmoplegia and/ or nystagmus), ataxia primarily affecting gait, and confusion or delirium. <sup>1,2</sup> More patients present atypically with disturbances of attention, impaired consciousness, and loss of ability to walk.
<b>Korsakoff syndrome</b>	<p>Chronic amnesia that can complicate unrecognized or undertreated Wernicke encephalopathy. The <i>Diagnostic and Statistical Manual of Mental Disorders</i>, Fifth Edition, lists these diagnostic criteria for substance-induced major or mild neurocognitive disorder, including alcohol-induced major or mild neurocognitive disorder:</p> <ul style="list-style-type: none"><li>A. The criteria are met for major or mild neurocognitive disorder.</li><li>B. The neurocognitive impairments do not occur exclusively during the course of a delirium and persist beyond the usual duration of intoxication and acute withdrawal.</li><li>C. The involved substance...and duration and extent of use are capable of producing the neurocognitive impairment.</li><li>D. The temporal course of the neurocognitive deficits is consistent with the timing of substance...use and abstinence (e.g., the deficits remain stable or improve after a period of abstinence).</li><li>E. The neurocognitive disorder is not attributable to another medical condition or is not better explained by another mental disorder.”<sup>3</sup></li></ul>

<sup>1</sup> McKeon et al, 2008. <sup>2</sup> Thomson et al, 2002. <sup>3</sup> American Psychiatric Association, DSM-5, 2013, p. 627–628.

4.1.2. Slingsdael Korsakoff Center

The Slingsdael Korsakoff Center in Rotterdam, the Netherlands, is one of ten Dutch long-term care facilities for patients with Korsakoff syndrome. Many of our patients

are referred to us by general and psychiatric hospitals in the Rotterdam region. The Center offers day care, observation and diagnosis, and specialized nursing home care. Slingsdael cooperates with other care facilities supporting similarly affected patients. Gerridzen and Goossensen (2014) conducted a retrospective study of the patients at another of the Dutch facilities, in Markenhof, Beekbergen. The authors reported that many of their patients had challenging behaviors, including poor awareness of illness, apathy, disinhibition, and sometimes aggression. These observations match our experience.

Before admitting patients to Slingsdael, our physicians and psychologists make a triage visit to the patients who probably have cognitive disorders related to Wernicke-Korsakoff syndrome. We find that disappointingly few patients have been appropriately treated with parenteral thiamine during their hospital stay. In fact, up to 90% of all patients whom our team visited between 2009 and 2013 had not been receiving adequate thiamine supplementation according to van den Brink and Jansen's guidelines on dosages and preparations (Day et al, 2013; Galvin et al, 2010; Thomson et al, 2002; van den Brink & Jansen, 2009). In their studies of patients who were referred to an inpatient psychiatry service for alcohol addiction disorders, Isenberg-Grzeda et al (2012, 2014) showed that diagnosis of Wernicke encephalopathy remains difficult and that patients are underdiagnosed and undertreated, even in countries that have national guidelines.

#### **4.1.3. Mental and motor symptoms**

Few studies have reported the temporal progression of the gait disturbances and other symptoms of Wernicke encephalopathy. In this case report we describe a man with Wernicke encephalopathy, followed by Korsakoff syndrome. One of our objectives is to detail how his mental symptoms and gait disturbances evolved over a lengthy follow-up. Our second objective is to increase early clinical suspicion of Wernicke encephalopathy in self-neglecting alcoholic patients with severe mental and mobility problems before the disorder progresses to Wernicke-Korsakoff syndrome.

### **4.2. CASE REPORT**

#### **4.2.1. Medical history**

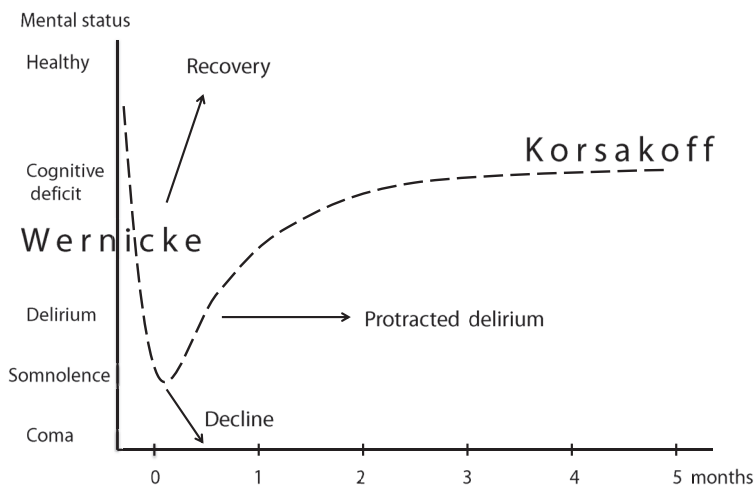
A 65-year-old man was transferred from a local Rotterdam hospital to the Slingsdael Korsakoff Center. He had been admitted to the hospital 24 days earlier for confusion and recent falls. He had a history of angina pectoris, hypertension, and a myocardial infarction seven years earlier. According to the hospital record, he had previously been smoking 20 cigarettes/day and drinking 2–3 bottles of wine/day and unknown quantities of beer and whiskey. The hospital treated him with a single 300 mg dose of IV

thiamine, followed by daily 100 mg thiamine tablets and vitamin B complex tablets.<sup>9</sup> When he was transferred from the hospital to the Slingsdael Korsakoff Center on day 24, he had a discharge diagnosis of “cognitive disorder due to alcohol abuse – probable Korsakoff syndrome.”

Following is a more detailed description of his course, starting with his admission to the local hospital.

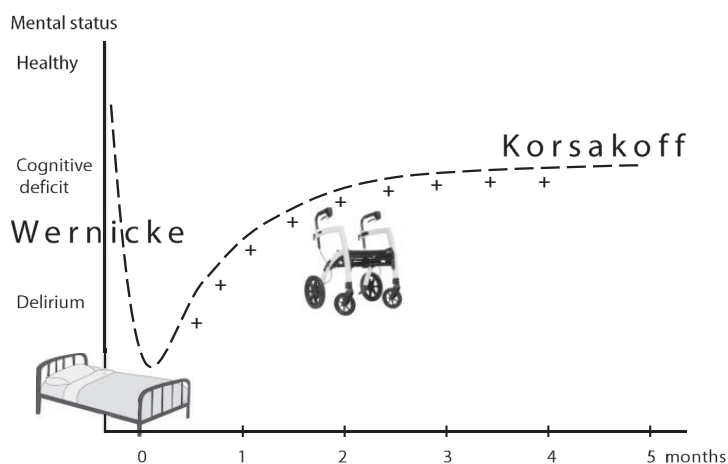
#### 4.2.2. Day 1 – Hospital admission

On admission, the patient looked disheveled and was reluctant to cooperate. He had impaired consciousness (Figure 4–1), with fluctuating drowsiness. He was bedridden because his poor balance had left him unable to walk (Figure 4–2). On the Glasgow Coma Scale (Teasdale & Jennett, 1974) he scored 12/15 for eye, motor, and verbal responses: ‘opens eyes in response to voice’ (grade = 3), ‘localizes painful stimuli’ (grade = 5), and ‘confused’ verbal responses (grade = 4). Neurologic examination of his cranial nerves was normal. His arms and legs showed no paralysis. His coordination and sensory functions could not be tested. His blood pressure was 120/90 mm Hg, pulse 100 beats/minute, peripheral oxygen saturation 100%, and body temperature normal.



**Figure 4–1.** The patient’s evolving neuropsychiatric symptoms of Wernicke-Korsakoff syndrome (dashed line), starting with initial hospitalization at 0 months. Arrows depict alternative outcomes: further decline, full recovery, or protracted delirium.

<sup>9</sup> According to Thomson et al (2009): “It seems unlikely that the oral route could provide the blood concentrations required in an emergency situation; this includes the ataxic and confused drunk [...] with the presentation of ‘collapse’. It has been shown that parenteral thiamine doses of up to 1 g may be required in the first 12 h.”



**Figure 4–2.** This patient’s evolving mobility as he moved through the neuropsychiatric stages (dashed line) of Wernicke-Korsakoff syndrome. For the first two weeks of his hospitalization, he was bedridden. From weeks 3 through 17, he walked with a walker (+ signs). Starting at week 18 (4 months), he was able to walk unaided.

Laboratory results: C-reactive protein 22 mg/L, hemoglobin 7.3 mmol/L, leukocytes  $8.8 \times 10^9/L$ , sodium 130 mmol/L, potassium 4.3 mmol/L, creatinine 52  $\mu\text{mol/L}$ , aspartate transaminase 52 U/L, alanine transaminase 42 U/L, gamma-glutamyl transpeptidase 322 IU/L, albumin 37 g/L, troponin < 20 ng/L, glucose 6.2 mmol/L, vitamin B<sub>1</sub> 25 nmol/L (reference range 70–140), and blood alcohol concentrations < 0.010% (0.1 g/L). Unfortunately, he was not tested for blood concentrations of other vitamins and micronutrients, such as niacin and magnesium.

An electrocardiogram showed sinus rhythm at 106 beats/minute, right bundle branch block, and no other abnormalities. Computed tomography imaging of the brain and duplex imaging of the carotid arteries (extracranial carotid circulation) did not reveal any abnormalities. Magnetic resonance imaging of the brain was impossible because of motion artifacts.

#### 4.2.3. Day 8

The patient scored 21/30 on the Mini-Mental State Examination (Folstein et al, 1975).

#### 4.2.4. Day 16

We visited the patient in preparation for transferring him to the Slingsdael Korsakoff Center. He told us that he had been admitted to the hospital after collapsing at the airport, and he could not remember what had happened since that day. He reported misusing alcohol since his youth. He told us he had recently reduced his drinking to about six pints of beer a day, and sometimes whiskey (he did not mention wine, which the hospital record showed he had also recently been abusing).

In the past few months he had been not eating well. He said that he had attended group sessions as part of an alcohol abuse treatment program, but he could not remember the exact details. He had completed intermediate school, and after training in several jobs, he had become an industrial foreman.

The patient was cooperative on examination. He sustained his attention relatively well, but his glazed eyes showed that he was not very alert. At first, his speech was slightly dysarthric, but it improved during the interview. Throughout the interview, he had mild difficulty finding words. His memory problems were obvious, and he was disoriented to time and place. He thought that he was in an office building near a bus station. He incorrectly assumed that he must have met one of us before. He had difficulty organizing his thoughts and he expressed himself incoherently. We were aware that he confabulated. He reported no hallucinations. His mood and affect appeared normal.

By now the patient could walk again with a walker and help from one person. In testing his coordination we found that his finger-to-nose test was normal but his heel-to-knee-to-toe test showed ataxia and hypermetria of both legs, left worse than right. We tested his eye movements by asking him to follow a slowly moving finger; his smooth pursuit was impaired in the right-horizontal direction. On admission to the Slingsdael Korsakoff Center, the patient showed fluctuating symptoms, with his confusion worsening in the late afternoon. He held attention fairly well (tenacity), but he was distracted by surrounding noises (hypervigilance). Numbness in both feet and reduced tendon reflexes indicated polyneuropathy.

#### 4.2.5. Day 24

He had normal laboratory test results for vitamin B<sub>6</sub>, B<sub>12</sub>, folate, and thyroid-stimulating hormone. His vitamin B<sub>1</sub> was 311 nmol/L (reference range 78–143). Because he had a vitamin D deficiency, with a serum (25OH) vitamin D of 25 nmol/L (reference range 50–150), we started him on oral cholecalciferol 100,000 IU bimonthly. By week 31 after his initial hospitalization, this treatment had brought his (25OH) vitamin D level up to 76 nmol/L.

**Table 4–2.** This patient’s test results during follow-up

	Week after hospital admission	Score	Interpretation
<b>Gait and balance</b>			
Performance Oriented Mobility Assessment <sup>a</sup>	4	12/28	High fall risk
	9	19/28	Medium fall risk
	17	22/28	Medium fall risk
	37	25/28	Low fall risk
<b>Muscle strength</b>			
Right quadriceps muscle maximum voluntary contraction	8	112 newtons	28% of 389 newtons <sup>b</sup>
	24	182 newtons	47% of 389 newtons <sup>b</sup>
<b>Neuropsychological tests</b>			
CAMCOG <sup>1</sup>		79/105	Impaired
Visual Association Test <sup>2</sup>		5/24	<1st percentile
Rey’s Verbal Learning Test <sup>3</sup>		2-1-3-3-3	<1st percentile
Stroop Color Word Test I <sup>4</sup>		53 seconds	12th percentile
Stroop Color Word Test II <sup>4</sup>	15	69 seconds	18th percentile
Stroop Color Word Test III <sup>4</sup>		120 seconds	21st percentile
Trail Making Test Part A <sup>4</sup>		54 seconds	16th percentile
Trail Making Test Part B <sup>4</sup>		131 seconds	4th percentile
BADS <sup>5</sup>		2-4-2-0-2-1	1st percentile

<sup>a</sup> Performance Oriented Mobility Assessment (Tinetti, 1986) is a task-oriented 16-item test that measures an adult’s gait and balance abilities. The total test score of 28 points combines the gait score (12 points) and the balance score (16 points). Fall risks in geriatric patients: low (25–28 points), medium (19–24 points), high (<19 points). <sup>b</sup> Reference value of 389 newtons related to sex, age, and body weight, described by Andrews et al, 1996. CAMCOG, the cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly. BADS, Behavioral Assessment of the Dysexecutive Syndrome. <sup>1</sup> Roth et al, 1992. <sup>2</sup> Lindeboom & Schmand, 2008. <sup>3</sup> van der Elst et al, 2005. <sup>4</sup> Schmand et al, 2004. <sup>5</sup> Maharasingam et al, 2013.

#### 4.2.6. Follow-up testing

Table 4–2 shows results of mobility, muscle strength, and neuropsychological testing done over most of the year after the patient’s hospital admission. After week 17 (4 months), he could walk independently without any aids. By his final test at week 37 (8.5 months), his risk of falling was low. His gait was wide-based, he spread his arms while walking, and his balance became more unsteady with eyes closed. Muscle strength tests done in weeks 8 and 24 showed improvement in his muscle strength. His weakness may have been caused by alcoholic myopathy.

During week 15, we gave the patient a full neuropsychological assessment. Clinically, he showed striking perseverations and confabulations. The assessment revealed disorders in orientation, memory, and executive functions, consistent with a developing Korsakoff syndrome.

At nine months after admission, he was still living at our Center and needing long-term nursing home care.

### **4.3. DIAGNOSTIC DIFFICULTIES**

#### **4.3.1. Reflection upon the case study**

Physicians run a risk of undertreating their patients – even hospitalized patients – who have alcohol-related disorders. During our patient's hospitalization, his symptoms were so unstable that a diagnosis of "probable" Korsakoff syndrome could not adequately explain them. With his history of alcohol dependence, he was in danger of suffering severe vitamin deficiencies (Sechi & Serra, 2007). He had arrived at the hospital in a somnolent state.

Two weeks later, he was in a transitional state, with his delirium partly in remission and his other symptoms fluctuating through the day: subnormal attention, memory deficits, disorientation, and mild language disturbances in the form of slight dysarthria and mild word finding difficulty. His positive symptoms that were consistent with Korsakoff syndrome were his memory deficits, disorientation, disturbances of time perspective, and confabulations.

#### **4.3.2. Neuropsychological profile of Korsakoff syndrome**

In general, Korsakoff syndrome is characterized by severe anterograde and, to a lesser extent, retrograde amnesia for declarative knowledge (Kopelman et al, 2009). Moreover, many patients have executive function deficits (Joyce & Robbins, 1991; van Oort & Kessels, 2008) such as problems with initiative, planning, organizing, and regulating behavior. Patients themselves are not tuned in to these problems because they have a limited awareness of their illness (Chapter 3). While patients with Korsakoff syndrome can exhibit confabulations (Bajo et al, 2010; Borsutzky et al, 2008; Kessels et al, 2008), these are also found in other neurologic conditions (Lorente-Rovira et al, 2011), and the intensity of confabulations may vary from one patient to another (Schnider, 2003).

Our patient's confabulations, along with his disturbances of memory and executive functions, make him look classic for Korsakoff syndrome (Kopelman et al, 2009; van Oort & Kessels, 2008). His clinical picture, however, was complicated by residual symptoms of Wernicke encephalopathy, most prominently mild attention difficulties, fluctuating symptoms, and worsening confusion in the late afternoon.

#### **4.3.3. Timing of Korsakoff diagnosis**

In most patients, Korsakoff syndrome can be diagnosed only after a four week (van den Brink & Jansen, 2009) to six week period of total alcohol abstinence (Goossensen et al,

2007). The diagnosis can take even longer in patients who have protracted delirium or repeated bouts of Wernicke encephalopathy. Although our patient was discharged from the hospital with a diagnosis of “probable” Korsakoff syndrome, his diagnosis could not be confirmed until several weeks later when his persistent attention deficit resolved. Because his symptoms were prematurely classified as “probable” Korsakoff syndrome, the real cause of his symptoms was overlooked. This may have led to the insufficient treatment of his initial Wernicke encephalopathy.<sup>10</sup>

## 4.4. DISCUSSION

### 4.4.1. Acute Wernicke phase

Alcoholic patients may be hospitalized for gradually worsening physical illness (Draper et al, 2011). However, many patients with Wernicke encephalopathy come to medical attention only after they collapse (Chapter 3). They may have been found on the ground or suddenly became bedridden within hours or days. According to autopsy-based series (Harper et al, 1986), the most common symptoms of Wernicke encephalopathy are mental status changes. The cognitive impairments range from apathy or mild confusion to severe coma (Donnino et al, 2007). Thomson et al (2002) showed that preceding Wernicke encephalopathy often goes unrecognized because it is atypical or incomplete. The diagnosis is also often missed because physicians have been led to believe that Wernicke encephalopathy is much rarer than it actually is, and so they are not looking for it (Cook, 2000).

### 4.4.2. Disturbances of gait

The physician may not be able to examine patients for signs of Wernicke encephalopathy if, like our patient, they are severely ill (Chapter 2; Donnino et al, 2007), bedridden, and unable to walk. Thus, it can be difficult to work through the extensive differential diagnosis of gait disorders in alcoholic patients. In addition to Wernicke encephalopathy, the more common possibilities include alcohol intoxication, central pontine myelinolysis, cerebellar atrophy, concussion, subdural hematoma and other processes that occupy intracranial space, polyneuropathy, myopathy, rhabdomyolysis, and cerebral vasculopathy of small vessels.

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10 According to British (Thomson et al, 2002), Dutch (van den Brink & Jansen, 2009), and European (Galvin et al, 2010) guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy.

### 4.4.3. Mental confusion

Further difficulty arises with syndromes that cause confusion, e.g., Wernicke-Korsakoff syndrome and delirium (Table 4–3). In a given patient, the physician may be challenged to distinguish among the possible syndromes and find the true underlying disorder, whether it is thiamine or niacin deficiency, alcohol withdrawal, or something else. Studies report that many patients with delirium tremens also have Wernicke encephalopathy

**Table 4–3.** Differential diagnosis of confusion, agitation, or drowsiness in patients with alcohol addiction

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#### Complications of alcohol abuse

Alcohol intoxication  
Alcohol withdrawal: delirium tremens, epilepsy  
Hypoglycemia, acidosis\*  
Electrolyte disorders: hyponatremia, hypomagnesemia

#### Acute or progressive cerebral disorders

Wernicke encephalopathy†  
Central pontine myelinolysis  
Head injury: subdural hematoma, concussion  
Stroke  
Intracranial space-occupying process  
Hepatic encephalopathy

#### Serious infections\*

Pneumonia, urosepsis, septicemia of unknown origin

#### Acute abdominal conditions

Gastrointestinal bleeding: ulcers, esophageal varices  
Portal hypertension, alcoholic hepatitis, cirrhosis  
Alcoholic pancreatitis  
Peritonitis associated with ascites  
Acute mesenteric ischemia, other vascular diseases‡

#### Decompensation in response to other conditions

Dysregulation in diabetes mellitus, dehydration  
Myocardial infarction, heart failure; cardiomyopathy\*  
Severe chronic obstructive pulmonary disease, emphysema, hypoxia, hypercapnia†  
Malignancy: mouth, throat, lung‡

#### Delirious state

May accompany all causes listed above

#### Other neuropsychiatric conditions

Korsakoff syndrome†  
Dementia  
Psychosis, schizophrenia  
Personality disorders, e.g., schizotypal, paranoid  
Depression and anxiety disorders

#### Other substance dependences or intoxications

Illicit drugs, benzodiazepines

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Conditions were collected from medical records of patients admitted to Slingsdael Korsakoff Center, Rotterdam, the Netherlands. \* Possibly caused by or in combination with thiamine deficiency. † Caused by thiamine deficiency. ‡ In combination with smoking.

(McKeon et al, 2008; Thomson et al, 2002). However, it would be more precise to say that we assume that a delirium can be an important presenting feature of Wernicke-Korsakoff syndrome (Chapter 3 & 5). In alcoholics with self-neglect, delirium may be synonymous with active Wernicke encephalopathy, and should be treated as such.

The manifestations of delirious states in Wernicke-Korsakoff syndrome may vary. Wyszynski and Wyszynski (2005) reported that most patients show attention disorders; however, Caulo et al (2005) found that, like our patient, some patients can maintain their attention fairly well. MacDonald et al (2009) presented a video of a patient who had severe ophthalmoplegia and prominent gait ataxia, but no apparent neurocognitive changes; the authors did not make clear how they had evaluated the patient's cognitive functions.

*Postscript.* Park et al (2014) presented a case study of Wernicke encephalopathy associated with malnutrition and nausea due to a neuroblastoma in a child showing gait disturbances, nystagmus, and dizziness, but no changes of his alertness.

## 4.5. ADEQUATE THIAMINE TREATMENT

### 4.5.1. Timely thiamine treatment

Because Wernicke encephalopathy is potentially life-threatening, patients with suspected disease must be evaluated and managed aggressively (McCormick et al, 2011). Even before the diagnosis is confirmed, we recommend starting adequate vitamin replacement (Thomson et al, 2002; Thomson & Marshall, 2006a, 2006b; van den Brink & Jansen, 2009), alcohol detoxification, alcohol abstinence, and continued assessment of developing symptoms.<sup>11</sup>

### 4.5.2. Recommendations for parenteral thiamine

The multidisciplinary Mental Health Care guideline on alcohol-related disorders (van den Brink & Jansen, 2009;<sup>12</sup> Table 4–4), initiated by the Dutch Association for Psychiatry, and organized by the Dutch Institute for Healthcare Improvement and the Institute of Mental Health and Addiction (Trimbos Institute), recommends immediate treatment with parenteral thiamine for alcoholics who present with self-neglect, cognitive impairment, and gait disorders or polyneuropathy. When other symptoms, e.g., altered consciousness or eye movement disorders, further raise suspicion of Wernicke encephalopathy, van den Brink and Jansen (2009) advise larger doses of thiamine, with treatment duration depending on the clinical course.

<sup>11</sup> Cf., results of the reexamination we did during our visit on the 16<sup>th</sup> hospital day.

<sup>12</sup> Available at [www.diliguide.nl/document/1820](http://www.diliguide.nl/document/1820).

**Table 4–4.** Wernicke encephalopathy (WE) Recommendations from guidelines on Alcohol-related disorders: English-language paraphrase from van den Brink and Jansen (2009)

Alcohol abusers		
	At high risk for WE	With suspected WE
<b>Diagnosis</b>		
Because of atypical presentation, WE is difficult to diagnose. Therefore, alcoholic patients should be treated immediately if they have:	<ul style="list-style-type: none"><li>-Self-neglect</li><li>-Cognitive impairment</li><li>-Gait disturbance</li><li>-Polyneuropathy</li></ul>	Significant acute or subacute impairment of: <ul style="list-style-type: none"><li>-Consciousness</li><li>-Cognition</li><li>-Gait</li><li>-Eye motility (nystagmus, double vision)</li></ul>
Consider WE in people with serious alcohol use disorders who have impaired consciousness, cognition, gait, or eye motility		
<b>Treatment</b>		
Give vitamins as shown. Test for and replenish deficiencies of sodium, magnesium, and phosphate	<b>For 3–5 days:</b> Thiamine* 250 mg once/day IM or IV  Vitamin B complex forte† once/day PO Vitamin C 500 mg once/day PO	<b>Days 1–3:</b> Thiamine* 500 mg IV (given slowly in 100 mL of normal saline solution) three times/day Vitamin B complex forte† three times/day PO Vitamin C 500 mg three times/day PO  <b>After Day 3:</b> If patient improves, switch to regimen for patients at high risk If patient does not improve, stop treatment and reconsider the diagnosis

\* In the Netherlands, thiamine is available in injection fluid 100 mg/mL ampoules of 1 mL. † Vitamin B complex forte tablets contain 200% of the daily recommended amounts of vitamins B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub>, B<sub>5</sub>, B<sub>6</sub>, B<sub>8</sub>, B<sub>11</sub>, and B<sub>12</sub>.

4.6. CONCLUSION

In summary, self-neglecting alcoholic patients who are bedridden may have severe illness and should be suspected of having Wernicke encephalopathy. If such patients exhibit delirium, impaired consciousness, or mobility changes, they should be managed as though they have Wernicke encephalopathy, to prevent further neurologic complications of thiamine deficiency.



# CHAPTER 5

## **Biomarkers of delirium as a clue to diagnosis and pathogenesis of Wernicke-Korsakoff syndrome**

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Original article

Keywords: Alcoholism, Delirium, Diagnosis, Microglia, Physiopathology, Thiamine deficiency, Wernicke encephalopathy, Wernicke Korsakoff syndrome

## ABSTRACT

*Background.* Wernicke encephalopathy (WE) and Korsakoff syndrome are considered to be different stages of the same disorder due to thiamine deficiency, which is called Wernicke-Korsakoff syndrome (WKS).

The earliest biochemical change is the decrease of  $\alpha$ -ketoglutarate-dehydrogenase activity ( $\alpha$ -KGDH) in astrocytes. According to autopsy-based series, mental status changes are present in 82% of WE cases. The objective of the present review is to identify possible underlying mechanisms relating the occurrence of delirium to WKS.

*Method.* Studies involving delirium in Wernicke-Korsakoff syndrome, however, are rare. Therefore, first, a search was done for candidate biomarkers of delirium irrespective of the clinical setting. Secondly, the results were focused on identification of these biomarkers in reports on WKS.

*Results.* In various settings, ten biochemical and/ or genetic biomarkers showed strong associations with the occurrence of delirium. For Wernicke-Korsakoff syndrome, three of these candidate biomarkers were identified, namely brain tissue cell counts of CD68-positive cells as a marker of microglial activation, high cerebrospinal fluid lactate levels, and MHPG, a metabolite of norepinephrine.

Based on current literature, markers of microglial activation may present an interesting pathoetiological relationship between thiamine deficiency and delirium in WKS.

*Conclusion.* In WKS cases, changes in astroglia and microglial proliferation were reported. The possible loss-of-function mechanisms following thiamine deficiency in WKS are proposed to come from microglial activation, resulting in a delirium in the initial phase of WKS.

## 5.1. INTRODUCTION

### 5.1.1. Wernicke encephalopathy

Wernicke encephalopathy is an acute neuropsychiatric syndrome due to brain lesions caused by high metabolic demands on already depleted intracellular vitamin B<sub>1</sub> (thiamine) stores (Thomson et al, 2002). This depletion can directly lead to a cellular energy deficit, focal acidosis, regional increase in glutamate, and ultimately cell damage and death, although in an early phase these deficits may be reversible when restoration of thiamine takes place (Thomson et al, 2006a). In thiamine deficiency, the earliest biochemical change is the decrease of  $\alpha$ -ketoglutarate-dehydrogenase activity ( $\alpha$ -KGDH) in astrocytes (Sechi & Serra, 2007). According to autopsy-based series, mental status changes are present in 82% of WE cases (Harper et al, 1986). Wernicke encephalopathy is a rather common condition in comparison with other neurological disorders (Sechi & Serra, 2007). In affluent countries, 90% of the cases of thiamine deficiency are associated with alcohol abuse (Thomson et al, 2002). While the classic clinical signs of Wernicke encephalopathy are well known, namely ocular motility abnormalities, ataxia of gait and mental status changes, many cases of Wernicke encephalopathy remain unrecognized because the complete triad of symptoms is present in only 16% of patients with Wernicke encephalopathy (Thomson et al, 2002; Harper et al, 1986). Another reason why Wernicke encephalopathy may be underdiagnosed is that symptoms can easily be mistaken for alcohol withdrawal delirium (Rosenbaum, 2003).

### 5.1.2. Mental confusion in Wernicke's

In the literature, the mental phenomenon of Wernicke encephalopathy is sometimes described as 'mental confusion' without precise definition or description of its features in detail. Wyszynski and Wyszynski (2005) described the Wernicke delirium component in the encephalopathic phase of thiamine deficiency with reference to a number of recognizable pathologic states, such as Wernicke encephalopathy, that may be associated with the occurrence of delirium (Adams & Victor, 1985a). In DSM-IV-TR terminology, the diagnosis is delirium due to thiamine deficiency. According to the diagnostic criteria, delirious symptoms tend to fluctuate over the course of the day (American Psychiatric Association, 2000) such that relatively lucid periods alternate with episodes of more severe symptoms. In most cases of Wernicke encephalopathy, patients show attention disorders (Wyszynski & Wyszynski, 2005), although the patients' attention occasionally is relatively well sustained (Caulo al, 2005).

### 5.1.3. Aim of the study

We hypothesize that the recognition of Wernicke encephalopathy may frequently be based on the correct recognition of symptoms of delirium in the initial stages of

Wernicke-Korsakoff syndrome. The aim of the study is to review the main candidate biomarkers of delirium in Wernicke-Korsakoff syndrome and other clinically related conditions as an aid to WKS diagnosis and as a possible clue to its pathogenesis. This review may be useful in clinical practice to foster early diagnosis and treatment of Wernicke-Korsakoff syndrome and other delirious states.

## 5.2. METHOD

### 5.2.1. Search strategy and selection criteria

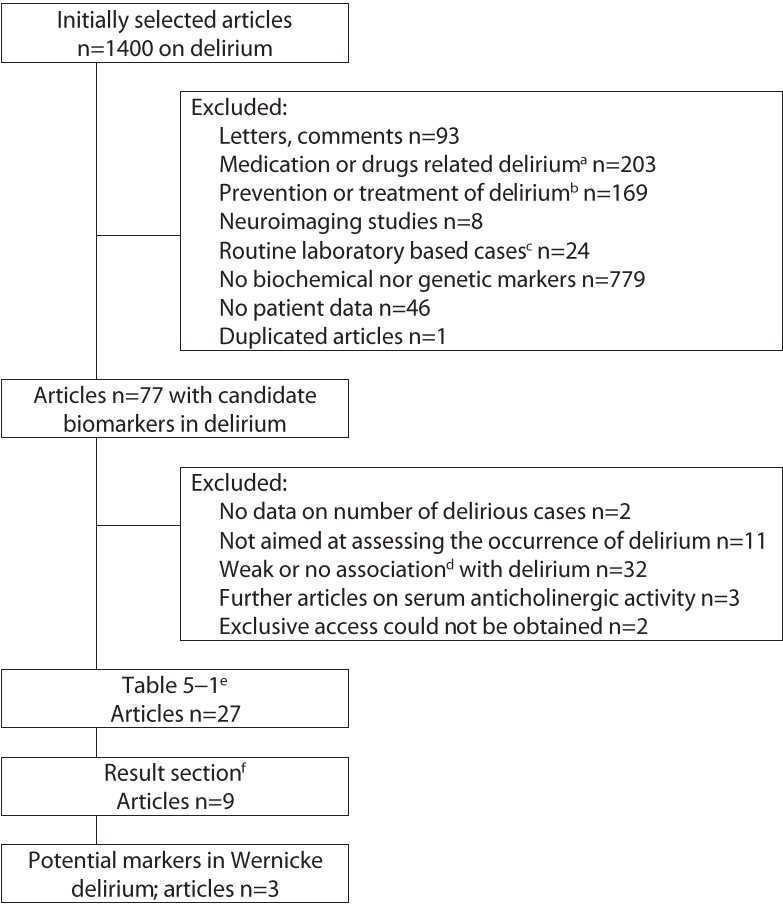
We conducted searches in PubMed, Cochrane Library, and PsycINFO for articles describing possible underlying causal mechanisms in delirium and alcohol withdrawal delirium (Figure 5–1) from January 1997 to December 2012. We searched for ‘delirium’ (Cochrane Library); ‘delirium’ and ‘biomarker/ biomarkers’ (PsycINFO); and by title (Delirium[ti]), Delirium[Mesh] terms (‘Delirium’, ‘Alcohol Withdrawal Delirium’, or ‘Delirium, Dementia, Amnestic, Cognitive Disorders’), and subheadings/ etiology, immunology, metabolism, pathology, physiopathology, or physiology (PubMed). The delirium studies were summarized and categorized by biomarker findings. We statistically identified studies where specific biomarkers were strongly associated with delirium. Subsequently, we searched for articles by < name of marker > and (‘Wernicke Encephalopathy’ [Mesh], ‘Korsakoff Syndrome’[Mesh] (PubMed); or ‘Wernicke’ (Cochrane Library; PsycINFO)). Studies comprising only small patient groups were also included. Application of more stringent criteria for selection of studies would compromise the number of biomarkers worthy of further consideration and review.

Studies on serum anticholinergic activity in the development of delirium were not taken into account, considering the test results of Cox et al (2009) who argued that previous research based on serum anticholinergic activity may need re-evaluation.

### 5.2.2. Statistics

Statistical effect size measures included standardized measures of effect such as odds ratios (OR) and effect-size correlations ( $r$ ).  $P$ -values and OR with corresponding 95%-confidence intervals (CI) were copied over from the original articles. Effect-size correlations with 95%-CI were calculated from descriptive statistic data, including means and standard deviations of the two groups (delirious patients versus non-delirious patients), if appropriate, and were weighted when the sample sizes were not equal. Associations are considered to be ‘positive’ if the mean difference is in the predicted direction, i.e., high levels of a substance corresponding with high frequency of delirium. When appropriate, ‘negative’ associations were described in terms of ‘low’ substance levels, ‘protective’ associations, or ‘decreased’ risk of delirium. The symbols + and ++ were used to describe

moderate and strong relationships with delirium respectively, irrespective of the positive or negative direction of the association. Studies presenting weak or no relationship with occurring delirium (OR between 0.5 and 2.0) or small magnitudes of group differences ( $r < 0.20$ , or  $\eta p^2 < 0.06$ ) were not included.



**Figure 5–1.** Flow chart of article selection

<sup>a</sup> Including substance-induced delirium, substance intoxication delirium, and substance withdrawal delirium, other than alcohol. <sup>b</sup> Including both medication and nonpharmacologic interventions. <sup>c</sup> Hypoxia, hemoglobin, mean corpuscular volume, blood platelet count, C-reactive protein, glucose, aspartate aminotransferase, bilirubin, creatine kinase, electrolyte disorders. <sup>d</sup> Studies presenting weak or no relationship with occurring delirium: odds ratio  $>0.5$  and  $<2.0$ , or small magnitudes of group differences (effect-size correlation ( $r$ )  $<0.20$ , or partial eta-squared ( $\eta p^2$ )  $<0.06$ ) were excluded. <sup>e</sup> Studies presenting moderate to strong relationship with delirium are summarized in Table 5–1. <sup>f</sup> Studies presenting strong relationship with delirium: odds ratio  $>5.0$  (or  $<0.2$ ), and large effect-size correlation ( $r$ )  $>0.50$  (or  $<-0.50$ ) are summarized in ‘Result section’.

### 5.3. RESULTS

#### 5.3.1. Studies selected

Five studies were related to delirium with alcohol withdrawal syndrome; 22 studies were related to delirium associated with other conditions (Table 5–1). With regard to the strength of the relationship between potential biomarkers and delirium, potential markers from nine articles showed strong relationships (++) with delirium, namely neuron-specific enolase (NSE) and S100B, catecholamine metabolites [homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenyl (ethylene) glycol (MHPG)], lactate in cerebrospinal fluid, and brain tissue cell counts of CD68-positive cells and of human leukocyte antigen-DR-positive cells (Grandi et al, 2011; van Munster et al, 2010a; van der Cammen et al, 2006; Nakamura et al, 2001; van Munster et al, 2011; Caplan et al, 2010).

Strong ‘protective’ associations with delirium were found in a glucocorticoid receptor type (Manenschijn et al, 2011) and in combined dopamine receptor and serotonin transporter types in alcohol withdrawal delirium (Karpyak et al, 2010). Strong opposite association were found in serum brain-derived neurotrophic factor (BDNF) in two different papers describing, among others, patients admitted to intensive care (Grandi et al, 2011) and patients suffering from alcohol withdrawal delirium (Huang et al, 2011). We did not find a clear explanation for substantial differences in magnitude of BDNF levels between the latter two studies.

#### 5.3.2. Neuron-specific enolase

Neuron-specific enolase (NSE) is an enolase-isoenzyme that is normally present in neuronal and neuroendocrine tissues. Lower levels of cerebrospinal fluid NSE were associated with occurrence of delirium (Caplan et al, 2010), in contrast with higher levels of serum NSE (Grandi et al, 2011). No studies were found that simultaneously measured NSE in cerebrospinal fluid and peripheral blood among patients with delirium.

#### 5.3.3. Other potential biomarkers

Van Munster et al (2010a) reported higher median levels of S100B in blood samples taken after delirium compared with levels in patients during delirium and in patients without delirium. No associations were found in S100B levels of delirious patients without dementia versus non-delirious patients with dementia (Caplan et al, 2010). Van der Cammen et al (2006) found that mean HVA levels were higher in delirious Alzheimer patients ( $195.0 \pm 101.0$  nmol/L) than in age- and gender-matched, non-delirious Alzheimer patients ( $68.3 \pm 33.2$  nmol/L). In patients undergoing cardiac surgery, Nakamura et al (2001) showed that, 1–2 days before operation, plasma levels of MHPG were higher in patients suffering from postoperative delirium ( $10.8 \pm 6.6$  ng/mL) than in the non-delirium group ( $5.3 \pm 3.7$  ng/mL). Compared with participants with dementia, patients

with delirium demonstrated higher cerebrospinal fluid lactate (mean  $1.87 \pm 0.31$  versus  $1.48 \pm 0.23$  mmol/L) (Caplan et al, 2010).

**Table 5–1.** Biomarkers in pathophysiology of delirium

Category	Estimate <sup>a</sup> [95%-CI]	Nº of patients <sup>b</sup>	Reference
<b>Candidate risk markers<sup>c</sup></b>			
- Serum cortisol levels*	Three levels, +, OR=3.1 [1.8–5.4], $P<0.001$	123/243 (51%)	Elective CABG surgery <sup>1</sup>
- Serum cortisol levels after dexamethasone suppression test (DST)	Means, mild vs. no delirium $r=0.25$ [0.10–0.39], $P=0.006$ ; moderate-severe vs. no delirium, +, $r=0.36$ [0.20–0.49], $P=0.01$	67/172 (39%)	Age <80, demented patients <sup>2</sup>
- Serum brain-derived neurotrophic factor, resp. neuron-specific enolase*	Means, +, $r=0.41$ [0.18–0.58], resp. ++, $r=0.98$ [0.97–0.99], $P<0.01$	30 delirious vs. 30 controls	Critically ill patients <sup>3</sup>
- Low plasma catalase levels	Means, +, $r=0.31$ [0.04–0.52], $P<0.035$	12/50	Patients undergoing cardiac bypass surgery <sup>4</sup>
<b>Candidate biomarkers<sup>d</sup></b>			
- Serum cortisol*	Three levels, +, OR=3.4 [1.7–6.8], $P=0.001$	73/164 (45%)	Critically ill patients after surgery <sup>5</sup>
- Log serum S100B protein*	+, OR=4.0 [1.9–8.6], $P<0.001$	62/120 (52%)	Age 65+, hip fracture surgery <sup>6</sup>
- Serum S100B protein* levels; highest levels after delirium	Median levels during delirium, after delirium, no delirium, $P=0.004$ ; after vs. no delirium, ++, $r=0.57$ [0.50–0.63] <sup>e</sup>	126/412 (31%)	Age 65+, acutely admitted medical patients <sup>7</sup>
- Low circulating insulin growth factor 1 (IGF-1)*	$r=0.28$ [0.03–0.49], $P=0.012$	22 with history of delirium / 57	Age 70+, admitted to Elderly Care Unit <sup>8</sup>
<b>Neurotransmitter precursors</b>			
- Low serum tryptophan (Trp) levels*	Means, +, $r=0.48$ [0.24–0.65], $P=0.001$	21/49	Age 50+, post-surgery, I.C. <sup>9</sup>
- Low plasma Trp*	$r=0.24$ [0.13–0.34], $P=0.005$	40/296	Age 25+, patients undergoing elective cardiac surgery <sup>10</sup>
- Low Trp / other LNAAs ratio	$r=0.22$ [0.10–0.32], $P=0.017$	(13.5%)	
<b>Neurotransmitter metabolites</b>			
- Homovanillic acid (HVA)	Means, ++, $r=0.65$ [0.42–0.78], $P<0.05$	17 delirious vs. 17 non-delirious	Patients suffering from Alzheimer's disease <sup>11</sup>
- Plasma 3-methoxy-4-hydroxyphenyl (ethylene) glycol (pMHPG)	++, $r=0.54$ [0.22–0.73], $P=0.08$	11/26	Patients undergoing operation for cardiovascular diseases <sup>12</sup>
<b>Inflammation-related</b>			
- Human herpes virus 6 reactivation	+, OR=2.5 [1.2–5.3], $P=0.02$	19/111 (17%)	Patients undergoing hematopoietic cell transplantation <sup>13</sup>

**Table 5–1.** Biomarkers in pathophysiology of delirium (continued)

Category	Estimate <sup>a</sup> [95%-CI]	Nº of patients <sup>b</sup>	Reference
- Serum interleukin-6 (IL-6)*; interleukin-8 (IL-8)	Median levels, $r=0.27$ [0.08–0.43] <sup>e</sup> , $P=0.01$ ; +, $r=0.33$ [0.14–0.48] <sup>e</sup> , $P=0.03$	50/98	Age 65+, hip fracture surgery <sup>14</sup>
- Serum IL-6*; IL-8	Detection level, +, OR=2.4 [1.03–5.6], $P=0.04$ ; OR=2.6 [1.06–6.3], $P=0.04$	64/185 (35%)	Age 65+, acutely admitted medical patients <sup>15</sup>
- Plasma neopterin	+, OR=3.8 [1.3–11], $P=0.02$	58 delirious vs. 67 controls	Age 70+, elective cardiac surgery: CABG, valve <sup>16</sup>
<b>Genetics</b>			
- Glucocorticoid receptor, homozygous Bc/I-Tth/III haplotype	++, protective† association with delirium, OR=0.08 [0.01–0.71], $P=0.029$	299/807 (37%)	Internal Medicine patients and (24.7%) hip fracture surgery <sup>17</sup>
- Dopamine transporter gene (solute carrier family 6, member 3) rs393795 homozygous AA genotype	+, protective† association with delirium, OR=0.4 [0.2–0.6], $P=0.0003$	558/1641 (34%)	Meta-analysis <sup>18</sup>
- Apolipoprotein E e4 allele* <sup>†</sup>	$r=0.21$ [0.07–0.34] <sup>9</sup> ( $P=0.005$ )	29/190 (15%)	Age 65+, major non-cardiac surgery <sup>19</sup>
<b>Postmortem brain tissue</b>			
- Human leukocyte antigen-DR resp. CD68 cell count <sup>h</sup> ;	Mean positive cell count, ++, $r=0.82$ [0.58–0.91] <sup>i</sup> resp. ++, $r=0.79$ [0.52–0.89];	9 cases (delirium), 6 controls	Age 60+, 7 cases and 4 controls dying with infection <sup>20</sup>
IL-6 immunoreactivity	Detection level, $P\leq 0.002$		
<b>Cerebrospinal fluid</b>			
- Interleukin-8 (IL-8)	Means, +, $r=0.48$ [0.40–0.67] <sup>i</sup> , $P=0.03$	15/36	Age 60+, hip surgery <sup>21</sup>
- Lactate; Protein; Lower levels of neuron-specific enolase	Means, ++, $r=0.58$ [0.34–0.73], $P<0.001$ ; +, $r=0.33$ [0.03–0.56], $P=0.036$ ; ++, $r=0.62$ [0.40–0.75], $P<0.001$	20 delirious vs. 20 Alzheimer's	Geriatric Medicine unit <sup>22</sup>
<b>Alcohol withdrawal</b>			
- Low serum brain-derived neurotrophic factor (BDNF)	Delirious vs. non-delirious alcoholics, ++, $r=0.71$ [0.58–0.79]; $P<0.001$ (three groups including controls)	25; 40; 39	Alcoholic cases, healthy controls <sup>23</sup>
- Combined DRD2 rs6276 G allele and SLC6A4 LL genotype	++, decreased† risk of delirium, OR=0.14 [0.04–0.52], $P<0.0001$ <sup>j</sup>	112/204	Alcohol-dependency <sup>24</sup>
- Dopamine transporter gene, A9 allele	+, OR=2.5 [1.1–5.8], $P=0.03$ <sup>k</sup>	34 <sup>k</sup> ; 86; 65 20/120 (17%) delirious	Alcohol-dependency <sup>25</sup>

**Table 5–1.** Biomarkers in pathophysiology of delirium (continued)

Category	Estimate <sup>a</sup> [95%-CI]	N <sup>o</sup> of patients <sup>b</sup>	Reference
- Dopamine transporter gene (DAT1); VNTR polymorphism in the 3' untranslated region of DAT1, nine-repeat allele	+, OR=2.4 [1.4–4.4], $P=0.003^k$	93 <sup>k</sup> ; 200; 93 59/293 (20%)	Alcohol-dependency <sup>26</sup>
- GRIK3 gene (Ser310Ala) coding for glutamatergic kainate receptor subunit GlurR7	$r=0.20$ [0.07–0.32] <sup>l</sup> , $P=0.008$	45/233 (19%) 233 alcoholics vs. 309 controls	Alcohol-dependency <sup>27</sup>

CABG, coronary artery bypass graft. I.C., Intensive Care unit. LNAAs, large neutral amino acids.

<sup>a</sup> Statistical association measures and 95%-confidence interval [95%-CI]: \* Similar studies presenting weak or no relationship with occurring delirium are not depicted. + moderate relationship (medium effect): odds ratio (OR) between 2.0 and 5.0 (†or between 0.2 and 0.5), ++ strong relationship (large effect): odds ratio >5.0 (†or <0.2), and effect-size correlation ( $r$ ): small 0.10, medium 0.30, and large 0.50, using the means and standard deviations of two groups (delirious patients, non-delirious patients), when available.

<sup>b</sup> N<sup>o</sup> of patients: delirious cases / total cases, or case–control matching: delirious cases; non-delirious cases; controls. <sup>c</sup> Risk markers before onset of delirium. <sup>d</sup> During or after delirium, or during postoperative period if applicable. <sup>e</sup> Effect size correlation ( $r$ ) based on conversion of data (median, interquartile range) to approximate mean and standard deviation. <sup>f</sup> Studies on APOE genotype and *duration* of delirium, are omitted. <sup>g</sup> Calculated from  $\chi^2$  and number of subjects in the study. <sup>h</sup> Markers for microglial activity. <sup>i</sup> Calculated from Z-score and number of subjects in the study. <sup>j</sup> Corrected for maximum alcoholic drinks/day. <sup>k</sup> Including alcohol withdrawal delirium *and/or* seizures. <sup>l</sup> Calculated from  $\chi^2$  and number of alcoholic subjects with/ without delirium tremens (excluding seizures).

References: <sup>1</sup>Mu et al, 2010. <sup>2</sup>Robertsson et al, 2001. <sup>3</sup>Grandi et al, 2011. <sup>4</sup>Karlidag et al, 2006. <sup>5</sup>Shi et al, 2010. <sup>6</sup>van Munster et al, 2010b. <sup>7</sup>van Munster et al, 2010a. <sup>8</sup>Adamis et al, 2007. <sup>9</sup>Robinson et al, 2008. <sup>10</sup>van der Mast et al, 2000. <sup>11</sup>van der Cammen et al, 2006. <sup>12</sup>Nakamura et al, 2001. <sup>13</sup>Zerr et al, 2011. <sup>14</sup>van Munster et al, 2008. <sup>15</sup>de Rooij et al, 2007. <sup>16</sup>Osse et al, 2012. <sup>17</sup>Manenschijs et al, 2011. <sup>18</sup>van Munster et al, 2010c. <sup>19</sup>Leung et al, 2007. <sup>20</sup>van Munster et al, 2011. <sup>21</sup>MacLulich et al, 2011. <sup>22</sup>Caplan et al, 2010. <sup>23</sup>Huang et al, 2011. <sup>24</sup>Karpyak et al, 2010. <sup>25</sup>Gorwood et al, 2003. <sup>26</sup>Sander et al, 1997. <sup>27</sup>Preuss et al, 2006.

### 5.3.4. Postmortem brain tissue

Expression of CD68 protein on microglia – used as a marker of microglial activation – was found higher in a postmortem study of septic patients compared with controls, indicating an enhanced immunological response in human brain tissue during systemic inflammatory reaction (Lemstra et al, 2007). Similar differences were observed in the postmortem case–control study of delirious patients and non-delirious controls (van Munster et al, 2011) regarding markers of microglial activation, including CD68 and human leukocyte antigen-DR expression. In this study of van Munster et al (2011), we calculated large effect-size measures in delirium associated with brain tissue cell counts of CD68-positive cells ( $r = 0.79$ , 95%-CI: 0.52–0.89) and human leukocyte antigen-DR-positive cells ( $r = 0.82$ , 95%-CI: 0.58–0.91).

### 5.3.5. Comparison with Wernicke-Korsakoff's

Subsequently, the focus was directed toward a systematic identification of aforementioned potential markers in delirium relating to Wernicke-Korsakoff syndrome. Search terms<sup>13</sup> including < *name of marker* > in articles on Wernicke-Korsakoff syndrome led to search results composed of a much reduced set of items, namely brain tissue cell counts of CD68-positive cells in an animal model (Wang & Hazell, 2010) and high cerebrospinal fluid lactate levels in six children suffering from Wernicke encephalopathy (Fattal-Valevski, 2005; Xin et al, 2011). As we were seeking biomarkers for delirium, findings of low MHPG concentrations in patients with long-standing Korsakoff's (Reuster et al, 2003) and descriptions of cerebrospinal fluid BDNF levels in alcohol-induced dementia were not taken into account (Blasko et al, 2006).

## 5.4. DISCUSSION

### 5.4.1. Introduction

Although delirium is a common syndrome, the pathophysiology of delirium remains poorly understood and its underlying mechanisms are largely unknown. The aim of the present study is to identify possible underlying mechanisms relating the occurrence of delirium to Wernicke-Korsakoff syndrome. The 'Result section' is initially framed by candidate biomarkers of delirium associated with alcohol withdrawal and other conditions. For the cases of Wernicke-Korsakoff syndrome, the selected biomarkers contained in the last paragraph of the 'Result section' might be of interest. Findings of CD68 as a marker of microglial activation are discussed in more detail in § 5.4.2. Increased lactate has been reported in thiamine deficiency, presumed secondary to the role of thiamine as a cofactor for the pyruvate dehydrogenase complex and  $\alpha$ -KGDH (Rodan et al, 2013).

### 5.4.2. Thiamine deficiency and microglial activation

For the most likely mechanisms of action, we would expect metabolic disturbances to contribute to the neuronal dysfunction observed in thiamine deficiency. In neuronal and glial cells, thiamine is converted to thiamine pyrophosphate, which is necessary for several biochemical pathways in the brain. It is well known that the earliest biochemical change in thiamine deficiency is the decrease in  $\alpha$ -KGDH activity in astrocytes. In Wernicke-Korsakoff patients, changes in astroglia together with microglial proliferation were apparent even in regions of the brain with little if any neuronal cell death (Sechi & Serra, 2007). Todd and Butterworth (1999) have identified activated microglia as a

13 Search terms: Brain-derived neurotrophic factor/ BDNF, CD68, dopamine, glucocorticoid, homovanillic acid/ HVA, human leukocyte antigen-DR, cerebrospinal fluid lactate, 3-methoxy-4-hydroxyphenyl (ethylene)glycol/ MHPG, neuron-specific enolase/ NSE, S100B, serotonin.

feature of thiamine deficiency, in which levels of CD11b/c (OX-42) and CD68 proteins, localized predominantly in these brain cells, were increased in early stages of the disorder before the development of neuronal cell death. Wang and Hazell (2010) suggested that microglial activation played a role in the development of neurological impairment in thiamine deficiency and possibly Wernicke encephalopathy. In their study of a rat model, symptoms of thiamine deficiency, among others loss of righting reflex, were assessed daily. The rats were killed at the loss of righting reflex stage, and brain tissue of three selected areas including vulnerable medial thalamus and inferior colliculus, and non-vulnerable frontal cortex, were examined. Expression of CD11b/c and CD68 mRNA was increased in the vulnerable brain areas in thiamine deficiency, compared with control animals. The experimental study of Wang and Hazell (2010) might therefore present a potentially interesting link between thiamine deficiency delirium in Wernicke encephalopathy and the possible implications of microglial activation in human brain diseases.

#### **5.4.3. Some further information on microglia**

Microglia are the third type of glial cell, along with astrocytes and oligodendrocytes (which together form the macroglia). Microglia vary in appearance depending on developmental stage, functional state, and anatomical location; subtype terms include ramified, perivascular, amoeboid, resting, and activated. Microglia clearly are capable of phagocytosis and play an important role in a wide spectrum of neuropathologies. They have also been suggested to act in several roles including in secretion (e.g., of cytokines and neural growth factors), in immunological processing (e.g., antigen presentation), and in central nervous system development and remodeling (Microglia, MeSH database. National Center for Biotechnology Information. [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)).

#### **5.4.4. Pathogenesis of delirium**

Although applying information from animal research to humans should be done with caution, many features of the rat/ mouse models of thiamine deficiency closely correlate with those seen in Wernicke encephalopathy (Vetreno et al, 2012). However, we don't know whether the biomarkers listed in this review, do provide an objective measure of disease pathophysiology in delirious patients. Instead, biomarkers may reflect:

- (i) general medical conditions, e.g., systemic infection with a concomitant delirium,
- (ii) a general state of arousal occurring during delirium, or
- (iii) stable trait characteristics originating from genetic factors, which influence the risk of delirium but are not directly involved in the acute process.

For an overview of brain pathology in thiamine deficient rodent models, the reader is advised to consult the Free PubMed Central paper of Vetreno et al (2012). Additional evidence on microglial activation in thiamine deficiency is found in studies of Calingasan et al (1999), Ke et al (2005), and Yang et al (2011).

## 5.5. CONCLUSION

In patients with Wernicke-Korsakoff syndrome, changes in astroglia together with microglial proliferation were reported (Sechi & Serra, 2007). According to autopsy-based series, mental status changes are present in 82% of Wernicke encephalopathy cases (Harper et al, 1986). Delirium is an important feature of Wernicke-Korsakoff syndrome, which may be related to microglial activation (Wang & Hazell, 2010) following thiamine deficiency.<sup>14</sup> Wernicke-Korsakoff syndrome is considered to be an example of delirium-related cognitive damage, presenting with delirium subsequently progressing to chronic cognitive impairment and in many instances irreversible brain damage. The current review suggests that<sup>15</sup> in self-neglecting alcoholic patients, recognition of delirium is an important clinical target in preventing further damage from the neurological complications of thiamine deficiency.

## 5.6. STRENGTH AND LIMITATIONS

We proposed a change of viewpoint in the diagnosis and therapeutic approach to Wernicke encephalopathy that recognizes the initial symptoms of thiamin deficiency overlapping with many symptoms of delirium and examines the interrelations between both delirium and cognitive deficit in Wernicke-Korsakoff syndrome.

No descriptions are given of how delirium was assessed in the original studies. From an etiological point of view, it is very unlikely that a single genetic or biochemical marker would account for most of the symptoms in delirious states. Although the biomarkers listed may have an association with delirium, evidence for causality is lacking. The review is based on limited selection criteria regarding the pathophysiology of delirium and may be prone to selection biases lacking data from grey literature or other articles describing loss-of-function mechanism in delirium.

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14 The effects of thiamine administration on cytokines and inflammatory markers in thiamine deficient patients are not yet known.

15 Postscript: "The current review suggests that...", might be rephrased as: With these results, we suggest that...

## 5.7. SUGGESTIONS FOR FUTURE RESEARCH

Future research focusing on strategies for the early identification of delirium in Wernicke-Korsakoff syndrome and assessment of the temporal progression of delirium including quantification of transitional stages and protracted or persistent delirium is recommended. Although our findings suggest that Wernicke delirium may represent the initial phase of Wernicke-Korsakoff syndrome due to mechanisms of microglial activation, extensive confirmation of this mechanism requires further research. In order to determine whether mediating factors in microglial activation other than thiamine deficiency, may account for an ineffective treatment of the more severe cases of Wernicke encephalopathy, further investigation is warranted.

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# CHAPTER 6

## **Cognitive effects of infections in Wernicke-Korsakoff syndrome**

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Critical Care (submitted)

Regular article

Key words: Infection, Inflammation, Wernicke Korsakoff syndrome, Thiamine deficiency, Memory disorders, Executive function, Critical illness

## ABSTRACT

*Background.* Acute Wernicke encephalopathy can have different clinical outcomes. While infections may precipitate the encephalopathy itself, it is unknown if infections also modify the long-term outcome in patients developing Korsakoff syndrome.

*Aim of the study.* To determine whether markers of infection such as white blood cell counts and absolute neutrophil counts in the acute Wernicke encephalopathy are associated with cognitive outcomes in the end-stage Korsakoff syndrome. We hypothesized that systemic infections in the acute Wernicke phase are associated with cognitive deficits in patients with Wernicke-Korsakoff syndrome.

*Method.* Retrospective, descriptive study of patients admitted to the observation department of Slingsdael Korsakoff Center, from February 1, 2012 to March 1, 2014, and patients of the residential care departments, at the set date of March 1, 2014. Hospital discharge letters of patients with an acute Wernicke encephalopathy were searched for relevant data on infections present upon hospital admission. Patients were selected for further analysis if the onset of the Wernicke-Korsakoff syndrome was clearly documented and if data were available on white blood cell counts in the acute phase and at least one of six predefined neuropsychological tests on follow-up.

*Results.* Infections were reported in 35/68 (51%; 95%-confidence interval: 41–62%) patients during the acute phase of WKS: meningitis (1), pneumonia (14), urinary tract infections (9), acute abdominal infections (4), sepsis (5) and/ or empyema (1), and infection 'of unknown origin' (4).

The neuropsychological test results showed significant lower scores on the Cambridge Cognitive Examination (CAMCOG) non-memory section with increasing white blood cell counts (Spearman's rank correlation,  $Rho = -0.34$ ; 95%-CI:  $-0.57$ – $-0.06$ ; 44 patients) and on the 'Key search test' of the Behavioral Assessment of the Dysexecutive Syndrome (BADS) with increasing absolute neutrophil counts ( $Rho = -0.85$ ; 95%-CI:  $-0.97$ – $-0.42$ ; nine patients).

*Conclusion.* Infections may be the presenting manifestation of thiamine deficiency. Wernicke-Korsakoff patients who suffered from an infection during the acute phase are at risk of worse neuropsychological outcomes on follow-up.

## 6.1. INTRODUCTION

### 6.1.1. Wernicke-Korsakoff syndrome

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 frequently originating from the lungs, liver cirrhosis, and the effects of irreversible thiamine deficiency (Adams & Victor, 1985b). If the acute phase of Wernicke encephalopathy is followed by chronic cognitive impairments of Korsakoff syndrome a Wernicke-Korsakoff syndrome can be diagnosed (Joyce & Robbins, 1991; Kopelman et al, 2009; Thomson et al, 2002; van Oort & Kessels, 2009). It is already well known that executive dysfunction, as well as memory dysfunction, is an important clinical feature of the Korsakoff syndrome (Kessels et al, 2008; Kopelman et al, 2009).

### 6.1.2. Infections and thiamine deficiency

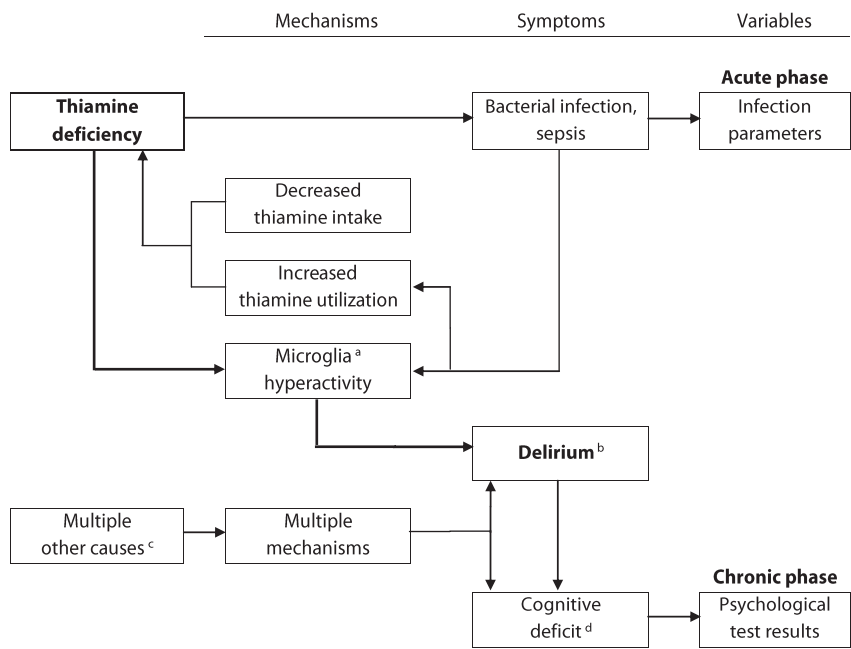
Recent literature suggests a complex interrelationship between infections and thiamine deficiency. Critically ill patients may present with thiamine deficiency or develop this deficiency during their acute illness (Donnino et al, 2010). Systemic infection is often revealed by or associated with brain dysfunction (Adam et al, 2013; Young, 2010; Schwalm et al, 2014) and Wernicke encephalopathy is one of the main differential diagnoses of infection-related encephalopathy (Adam et al, 2013).

In thiamine deficiency, infections may be both a presenting symptom and a complicating factor. According to pediatric literature, infections can be a heralding sign of severe thiamine deficiency, as shown in infants with thiamine deficiency presenting with infections and lactic acidosis (Fattal-Valevski et al, 2005; Xin et al, 2011). Having an infection, moreover, can increase the utilization of thiamine and may precipitate Wernicke encephalopathy in patients with marginal thiamine reserves (Donnino et al, 2007; World Health Organization, 1999).

Although many studies described the transition of Wernicke encephalopathy to Korsakoff syndrome (Harper et al, 1986; Kopelman et al, 2009; Sechi & Serra, 2007; Thomson & Marshall, 2006a), the possible role of systemic infections in this transition is not clear.

### 6.1.3. Aim of the study

Based on the relation between thiamine deficiency and infections, we hypothesized that infections may be associated with the severity of cognitive deficits in WKS patients (Figure 6–1; van Gool et al, 2010; Wang & Hazell, 2010). The research questions were: How common were infections in the initial phase of Wernicke-Korsakoff syndrome? Were white blood cell (WBC) counts and absolute neutrophil counts (ANCs) related to the cognitive outcomes?



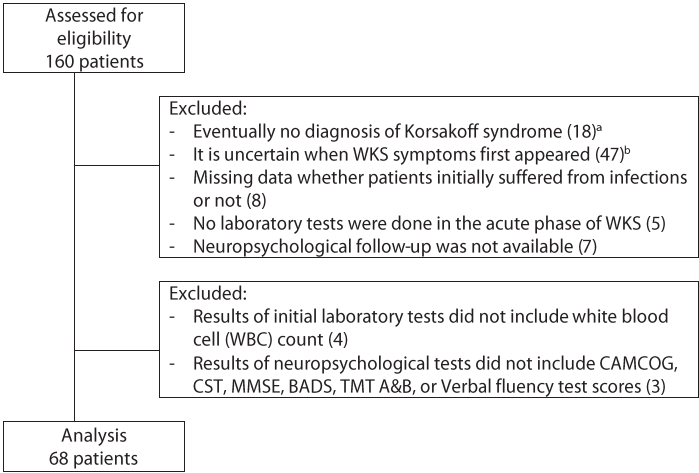
**Figure 6–1.** Interdependency of infections and Wernicke-Korsakoff syndrome

<sup>a</sup> Microglial cells of the brain. Wang and Hazell (2011) observed induction of microglial activity in their thiamine deficient rodent model. Based on an hypothesis of van Gool et al (2011) systemic infections may cause microglial hyperactivity leading to a delirium. <sup>b</sup> Delirium due to thiamine deficiency = Wernicke encephalopathy. <sup>c</sup> Electrolyte disorders, alcohol withdrawal, hepatic failure, renal failure, brain injury, etcetera. <sup>d</sup> Neurocognitive disorder due to thiamine deficiency = Korsakoff syndrome.

6.2. METHOD

6.2.1. Study design and subjects

In this 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. Inclusion criteria for the present analysis were: a diagnosis of Wernicke-Korsakoff syndrome with complete data on white blood count during the preceding acute phase and availability of predefined neuropsychological test results during follow-up, including cognitive screening tests and/ or more extensive neurocognitive tests. Data collection involved the patients’ age, sex, body mass index, and alcohol use. Laboratory results consisted of routine biochemical and hematological testing from the previous hospital setting. Developing WKS symptoms were categorized as: ‘vomiting’ (Moulin et al, 2014), ‘drowsiness’ (Fei et al, 2008), ‘confusion’, ‘walking disability’, or ‘collapse’ if the patient was found on the floor. Reasons of exclusion from the present analysis are summarized in Figure 6–2.



**Figure 6–2.** Flow chart 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. <sup>a</sup> Dementia (9 patients), acquired brain injury (3), hepatic encephalopathy (1), minimal or atypical cognitive symptoms (1), other (4). <sup>b</sup> 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), gradual deterioration over time (4).

6.2.2. Infection diagnoses

In this 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, urinary tract infections) that were present upon admission in the acute phase, according to the reports on the diagnostic work-up including blood tests, chest films, bacterial cultures, or any other information. We extracted data on body temperature, heart rate, and/ or blood pressure, if available.

6.2.3. Neuropsychological tests

Psychological test scores were obtained from neuropsychological tests that were administered in the post-acute phase after hospital discharge and at least six weeks of alcohol abstinence. We recorded the results of six predefined tests, including Cambridge Cognitive Examination (CAMCOG; Roth et al, 1992), Mini-Mental State Examination (MMSE; Folstein et al, 1975), Cognitive Screening Test (CST; de Graaf & Deelman, 1991), Behavioral Assessment of the Dysexecutive Syndrome (BADS; Maharasingam et al, 2013), Trail Making Test A&B (TMT; Schmand et al, 2004), and Verbal fluency test, if available. Because of the different aspects of cognition, we chose to separately examine subtest scores of the Cambridge Cognitive Examination (CAMCOG) and of the Behavioral Assessment of the Dysexecutive Syndrome (BADS).

**Table 6–1.** Patients referred to Slingsdael Korsakoff Center

Characteristics	N <sup>a</sup> (%)	Mean (SD)
Age (year)		
Male	132	59 (8)
Female	28 (18%)	58 (9)
BMI (kg/m <sup>2</sup> )		
Male	119 <sup>a</sup>	23.1 (4.1)
Female	25 <sup>a</sup>	23.0 (5.4)
Alcohol use (mL/d) <sup>b</sup>		
Male	69 <sup>c</sup>	240 (170)
Female	16 <sup>c</sup>	200 (103)
Prior diagnostic setting <sup>d</sup>		
Inpatient, general hospital	99 (62%)	
Inpatient, mental health care	26 (16%)	
Outpatient, ambulatory	32 (20%)	
Missing data	3 (2%)	
Referred to Slingsdael by <sup>e</sup>		
General hospital	62 (39%)	
Mental health care <sup>f</sup>	61 (38%)	
Other <sup>g</sup>	37 (23%)	

N<sup>a</sup>, number of patients. <sup>a</sup> Missing data in the other male/ female patients. <sup>b</sup> Quantity of pure alcohol (mL/d): beer 250 mL = 12.5 mL pure alcohol, wine 100 mL = 12 mL pure alcohol, liquor 35 mL = 12.25 mL pure alcohol. <sup>c</sup> Unspecified as 'alcohol abuse' in the other patients. <sup>d</sup> Diagnostic setting, in which Korsakoff syndrome was diagnosed or strongly suggested. <sup>e</sup> Following hospitalization, patients may have been admitted to a care facility elsewhere or discharged home, before being referred to Slingsdael Korsakoff Center. <sup>f</sup> Psychiatric hospital, psychiatric department, alcohol clinic, ambulatory mental health care. <sup>g</sup> Nursing home, GP, homeless shelter, and other.

#### 6.2.4. Statistical tests

The unpaired Student's t-test was used to compare laboratory results of patients with and without infections. Associations between white blood cell count and cognitive scores were explored with plots and Spearman's Rho coefficients with 95%-confidence intervals (95%-CI). The statistical analyses were conducted with SPSS, version 21.

### 6.3. RESULTS

#### 6.3.1. Patient characteristics

Patient characteristics are shown in Table 6–1. All patients had at least two or more symptoms according to the DSM-5 diagnostic criteria of alcohol use disorder (American Psychiatric Association, 2013, p. 490–491). Malnutrition was recorded in 55/68 patients.

The WKS symptoms developed within median 3.5 days (interquartile range [IQR] 1–14 days) before hospital admission. Symptoms were vomiting in 6/68 (9%) patients, drowsiness in 12 patients (18%), confusion in 48 patients (71%), walking disability in 19 (30%), and/ or collapse in 8 (12%).

6.3.2. Infections and laboratory results

Infections were present in 35/68 (51%; 95%-confidence interval: 41–62%) patients during the initial phase of WKS. No focus was found in 4/35 patients. The main sites of the infections are given in Table 6–2. In 2/35 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, e.g., anemia, electrolyte disorders, renal dysfunction, liver dysfunction, and vitamin deficiencies (Table 6–3).

**Table 6–2.** Infection diagnosis in patients referred to Slingsdael Korsakoff Center

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

6.3.3. 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 (IQR 2.5–8 months). CAMCOG total scores were available in 45/68 patients, CAMCOG non-memory scores in 44/68 patients, MMSE scores in 60/68 patients; the other numbers are given in Table 6–4. Overall, the correlation coefficient calculated from white blood cell (WBC) counts and neuropsychological test scores was negative, indicating more impairments on follow-up with increasing white blood cell counts in the acute phase, for almost all cognitive test scores (Table 6–4).

The correlation was statistically significant for the non-memory section of the Cambridge Cognitive Examination (CAMCOG) ( $Rho = -0.34$ ; 95%-CI:  $-0.57$ – $-0.06$ ; 44 patients).  $Rho$  calculated from absolute neutrophil counts (ANCs) and neuropsychological test scores was significant for the ‘Key search test’ of the BADS ( $Rho = -0.85$ ; 95%-CI:  $-0.99$ – $-0.44$ ; 9 patients, Figure 6–3).

**Table 6–3.** Laboratory results subdivided by initial infection status

Results, mean (SD)	N <sup>a</sup>	With infection <sup>a</sup>	N <sup>a</sup>	Without infection	Reference value	P value <sup>b</sup>
WBC count, / $\mu$ L	35	13200 (5200)	33	9400 (2700)	3500–10000	<0.001
ANC, / $\mu$ L	8	11200 (4300)	10	5100 (2400)	1500–8000	0.002
CRP, mg/L	23	58 (55)	19	20 (35)	<10	0.014
ESR, mm/h	13	62 (37)	13	28 (24)	<20	0.011
Hb, g/dL	26	13.9 (3.1)	27	13.6 (2.1)	14–17.5	0.73
Creatinine, mg/dL	23	1.2 (0.75)	26	0.9 (0.41)	0.6–1.2	0.08
MDRD, mL/min/1.73m <sup>2</sup>	23	92 (55)	26	106 (38)	>90	0.32
Sodium, mEq/L	25	137 (7)	26	134 (10)	136–145	0.40
Potassium, mEq/L	25	3.9 (0.8)	26	4.0 (0.7)	3.5–5.1	0.46
Albumin, g/dL	20	3.3 (0.9)	12	3.8 (0.6)	3.5–5.0	0.071
AST, U/L	23	77 (63)	22	80 (86)	<30	0.80 <sup>c</sup>
GGT, U/L	22	189 (179)	24	171 (195)	<35	0.82 <sup>c</sup>
Vitamin B <sub>12</sub> , $\mu$ g/dL <sup>d</sup>	7	1.7 (1.3)	10	2.2 (1.0)	2.4–4.7	0.41
25(OH)D, ng/mL	4	5 (3)	8	11 (10)	20–60	0.27
BAC, ‰	10	<0.1 (0.06)	9	<0.5 (1.1)	<0.1	0.28

N<sup>a</sup>, number of patients. WBC, white blood cell; ANC, absolute neutrophil count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; MDRD, estimate of glomerular filtration rate (eGFR) based on Modification of Diet in Renal Disease Study; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase, 25(OH)D, 25-hydroxyvitamin D; BAC, blood alcohol concentrations. <sup>a</sup>Infections occurred in 35/68 (51%; 95%-CI: 41–62%) patients. <sup>b</sup>Student's t-test P values of laboratory results are based on results of patients with and without infections. <sup>c</sup>P value based on <sup>10</sup>log of results (right skewed distribution of laboratory results). <sup>d</sup>1  $\mu$ g/dL = 10 ng/mL.

SI conversion factors: To convert Hb to Fe mmol/L, multiply values by 0.6206; to convert creatinine to  $\mu$ mol/L, multiply values by 88.4; to convert vitamin B<sub>12</sub> to nmol/L, multiply values by 29.6; to convert 25(OH) vitamin D to nmol/L multiply values by 2.496.

### 6.3.4. 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 clinical relevant abnormalities were found – the initial body temperature was 85.6–101.1 °F, heart rate 70–126 beats/minute and systolic blood pressure 89–175 mmHg, as far as described in the hospital discharges letters (< 30 patients).

**Table 6–4.** Neuropsychological test scores subdivided by initial infection status<sup>a</sup>

Results, mean (SD)	N <sup>o</sup>	With infection	N <sup>o</sup>	Without infection	Reference value	Rho <sup>b</sup>	95%-CI
CAMCOG total score	28	74.8 (10.5)	17	76.1 (9.6)	76–105	-0.17	-0.44–0.12
Non-memory section	27	53.1 (6.1)	17	57.2 (8.3)		-0.34	-0.57–0.06*
MMSE	33	21.9 (4.8)	27	21.8 (3.8)	24–30	-0.05	-0.29–0.20
CST-20	9	13.1 (3.3)	14	11.8 (4.9)	16–20	-0.05	-0.44–0.32
BADS total score	17	12.4 (3.3)	13	12.2 (4.2)	13–24	-0.20	-0.57–0.22
BADS Key search test	20	1.4 (1.4)	17	2.0 (1.4)		-0.26	-0.55–0.08
TMT A, percentile	20	15 (17)	25	11 (23)	>8	-0.04	-0.33–0.27
TMT B <sup>c</sup> , percentile	19	18 (24)	25	12 (22)	>8	0.05	-0.26–0.33
Verbal fluency test <sup>d</sup>	26	14.8 (6)	28	16.5 (7)	>14	-0.23	-0.49–0.05

N<sup>o</sup>, number of patients. CI, Confidence interval. \*  $P < 0.05$ . CAMCOG, Cambridge Cognitive Examination; MMSE, Mini-Mental State Examination; CST, Cognitive Screening Test; BADS, Behavioral Assessment of the Dysexecutive Syndrome consisting of six subtests; TMT, Trail Making Test A&B. <sup>a</sup> Infections occurred in 35/68 (51%; 95%-CI: 41–62%) patients. <sup>b</sup> Spearman's rank correlation coefficient (Rho) was calculated from white blood cell (WBC) counts and neuropsychological test scores, with 95%-confidence intervals. 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, 0.75–1 very strong. Negative coefficients reflect negative correlations, i.e., when test scores tend to decrease as WBC counts increase. <sup>c</sup> Ceased in 8/44 patients, resulting in 0 percentile score. <sup>d</sup> Category fluency test, naming animals in one minute.

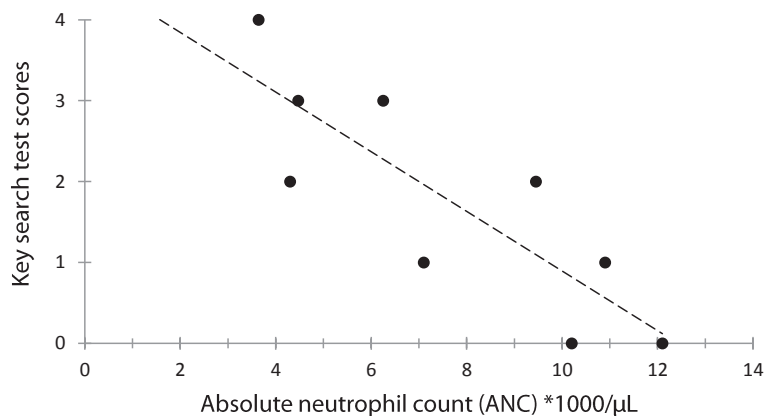
## 6.4. DISCUSSION

### 6.4.1. Infections in Wernicke-Korsakoff syndrome

In the acute phase of the alcohol-related Wernicke-Korsakoff syndrome, serious infections were present in our patient group.<sup>16</sup> 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 non-memory section with increasing white blood cell (WBC) counts, and of the 'Key search test' of the BADS with increasing absolute neutrophil counts (ANCs). Thus, differences in neuropsychological test scores were mainly observed in only two non-memory subtests of the six preselected neuropsychological tests. These results might give some indication that delirium and comorbid infections are associated with worse cognitive outcomes in Wernicke-Korsakoff syndrome.<sup>17</sup> Although these preliminary results should be interpreted with great caution, we suggest that possible

16 'Infections' refer to diagnoses listed in the patients' hospital discharge letters.

17 In dementia, the contribution of infection-related delirium to cognitive outcomes is not well known either. Risk markers for delirium, including biomarkers such as cytokines and proteomics, are being examined in the SAGES study (Schmitt EM, Marcantonio ER, Alsop DC, Jones RN, Rogers SO Jr, Fong TG, Metzger E, Inouye SK; SAGES Study Group. 2012. Novel



**Figure 6-3.** Trend between ANC and Key search test

----- is linear trend

cognitive effects of systemic inflammation in Wernicke-Korsakoff syndrome can be interpreted in terms of a differential vulnerability of brain areas involved in executive functioning and those involved in memory function.

#### 6.4.2. Thiamine deficiency and sepsis

Sepsis was reported in five 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 (Hansen et al, 1984). Remarkably, infection ‘of unknown origin’ was reported in 4/35 patients. We wondered whether these cases might reflect unidentified sepsis of unknown origin?

#### 6.4.3. Recent literature on thiamine deficiency and sepsis

Thiamine deficiency may be highly prevalent in septic patients as described in a study of serum thiamine, oxidative stress, and hospital mortality in adult patients with septic shock (Costa et al, 2014).<sup>18</sup> Of these patients, 77/108 (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

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risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *J Am Med Dir Assoc.* 13:818.e1–10).

18 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.

studies of critical illness in adults and children have shown that absolute or relative thiamine depletion was associated with an almost 50% increase in mortality (Manzanares & Hardy, 2011). Also, serum thiamine levels were not associated with protein carbonyl concentrations of serum samples, as markers of oxidative stress or protein damage.<sup>19</sup> In another study, 6/30 (20%) of septic patients had absolute thiamine deficiency, defined as serum thiamine concentrations of  $\leq 9$  nmol/L (Donnino et al, 2010). Three of these patients had absolute thiamine deficiency upon presentation and three patients developed absolute thiamine deficiency within 72 hours; with thiamine levels measured at intervals of 24 hours. None of 30 control patients (0/30, 0%) showed absolute thiamine deficiency.

In a mouse model of sepsis, de Andrade et al (2014) concluded that thiamine deficient food (TD) was associated with oxidative stress and inflammatory response changes. The septic condition included cecal ligation and puncture (CLP) thus exposing the abdominal cavity to fecal contamination. Total white blood cell counts and absolute neutrophil counts were the highest in the septic condition (CLP) with thiamine deficient food, but differences were significant for mononuclear cell counts. Interleukin-6 (IL-6) blood levels tended to be higher in CLP. Higher liver 4-hydroxy 2-nonenal (4-HNE;  $C_9H_{16}O_2$ ) levels were associated with oxidative stress in TD.

## 6.5. STRENGTH AND LIMITATIONS

We provided the first direct indication that systemic infections in the acute Wernicke phase might be associated with the long-term cognitive deficits in Wernicke-Korsakoff syndrome. 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 Wernicke-Korsakoff syndrome.

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, while thiamine deficiency and sepsis may be associated with various degrees of acidosis (Andersen et al, 2013; Donnino, 2010; Fattal-Valevski et al, 2005; Xin et al, 2011).

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19 Protein carbonylation; the appearance of carbonyl groups, such as aldehyde or ketone groups, in proteins as the result of several oxidative modification reactions. It is a standard marker for oxidative stress.

Secondly, possible covariates of white blood cell counts, e.g. smoking, amount of stress, or thiamine deficiency itself, were not taken into account. It is not yet clear to what extent elevated white blood cell counts do reflect the presence of infections in Wernicke-Korsakoff syndrome in those cases where no infections were found.

Furthermore, no corrections were made for the effect on cognitive outcomes of factors like education or age. Due to lack of detailed data, no analysis could be made of the severity of thiamine deficiency, severity of infections and subsequent inflammation, critical illness, or number of Intensive Care admissions.

## 6.6. CONCLUSIONS

In the literature there is limited information available regarding the incidence of infections in the initial stages of Wernicke-Korsakoff syndrome or the effects of inflammation on the ultimate Korsakoff syndrome.<sup>20, 21</sup> Infections can be a heralding sign of severe thiamine deficiency and Wernicke encephalopathy.<sup>22</sup> Patients who suffered from an infection during the acute phase of Wernicke-Korsakoff syndrome are at risk of worse neuropsychological outcomes.

## 6.7. SUGGESTIONS FOR FUTURE RESEARCH

The interrelationship of infections and thiamine depletion may represent a relevant area for further research in critically ill patients (Manzanares & Hardy, 2011; Ramsi et al, 2014).

- 20 Infection: Invasion of the body by microorganisms that can cause pathological conditions or diseases.
- 21 Inflammation: A pathological 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).
- 22 *Post-hoc analysis.* In this Chapter, we described the association between infections and thiamine deficiency in patients with Wernicke-Korsakoff syndrome without going into detail on the frequency of delirium. Although delirium may more frequently occur during infections, a post-hoc analysis of the data of the study shows no striking difference between the number of delirious patients with and without infections:

**Table.** Delirium and infection in 160 patients

N <sup>o</sup>		Infection		
		Yes	No	N/A
Delirium	Yes	36	32	6
	No or N/A	26	31	29

N<sup>o</sup>, number of patients. N/A, not mentioned.

Early and adequate thiamine supplementation could be helpful to self-neglecting alcoholic patients presenting with infections, confusion, drowsiness, or walking disability. 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.



# CHAPTER 7

## **Is vitamin D deficiency a confounder in alcoholic skeletal muscle myopathy?**

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Original research

Keywords: Alcoholism, Vitamin D deficiency, Alcohol-related disorders, Myopathy, Muscular atrophy

**ABSTRACT**

*Background.* Excessive intake of alcohol is often associated with low or subnormal levels of vitamin D even in the absence of active liver disease. As vitamin D deficiency is a well-recognized cause of myopathy, alcoholic myopathy might be related to vitamin D deficiency. Chronic alcoholic myopathy affects approximately half of chronic alcoholics and is characterized by the insidious development of muscular weakness and wasting. Although alcohol or its metabolites may have a direct toxic effect on muscles, the relationship between alcoholic myopathy and vitamin D deficiency has not been examined extensively.

*Method.* We reviewed articles on alcoholic myopathy and hypovitaminosis D myopathy and compared the pathophysiological findings to designate possible mechanisms of vitamin D action in alcohol-related myopathy.

*Results and Conclusion.* Given the strong interdependency of suboptimal levels of vitamin D, phosphate, and magnesium in chronic alcohol abuse, we hypothesize that combined deficiencies interfere with membrane and intracellular metabolic processes in alcohol-related chronic myopathy; however it is not yet possible to define exact mechanisms of interaction.

## 7.1. INTRODUCTION

### 7.1.1. Alcohol-related myopathy

Alcohol may cause either a life-threatening, acute myopathy, or a subacute to chronic myopathy (Slavin et al, 1983). The acute form probably results from a direct toxic effect of ethanol, acetaldehyde, or other ethanol metabolites. The chronic syndrome is characterized by an insidious development of muscular weakness and wasting (Diamond & Messing, 1994; Preedy & Peters, 1994; Slavin et al, 1983). Most of the literature examining the effect of alcohol abuse and vitamin D has been in alcohol-related osteopenia and osteoporosis, but vitamin D status in patients with muscle weakness associated with alcoholism is scarcely reported and sometimes even contradictory. In an earlier study by Hickish et al (1989), muscle weakness in male alcoholic patients appeared to be not significantly related to vitamin D deficiency. In a murine model of alcoholic myopathy, González-Reimers et al (2010) found that low vitamin D levels were related to muscle fiber atrophy, and altered levels of muscle antioxidant enzymes could play a role in alcoholic myopathy.

### 7.1.2. Aim of the review

We compared literature on 'alcoholic myopathy' and 'hypovitaminosis D myopathy' in order to designate possible mechanisms of vitamin D action in chronic, alcohol-related myopathy.

## 7.2. SEARCH STRATEGY AND SELECTION CRITERIA

We conducted a search in PubMed for articles from January, 1985 to September, 2011. We used the search terms: alcohol + myopathy (or sarcopenia, muscle weakness[MeSH], muscle strength[MeSH], falls), and vitamin D + myopathy (or sarcopenia, muscle weakness[MeSH], muscle strength[MeSH], falls) and identified English articles related to alcoholic myopathy or hypovitaminosis D myopathy on basis of titles and abstracts. Studies on vitamin D deficiency in alcoholism were found with combinations of the key words [MeSH]: alcoholism, alcohol drinking, vitamin D, and vitamin D deficiency. Additional articles were identified by means of reference lists. Studies involving animal case histories, and cardiac or smooth muscles, but not skeletal muscles, were excluded.

The concentrations of 25-hydroxyvitamin D (25(OH)D) were defined as insufficient when less than 50 nmol/L (1 nmol/L 25(OH)D = 0.4 ng/mL), deficient when less than 25 nmol/L, and severely deficient when less than 12.5 nmol/L (Bang et al, 2009).

### 7.3. ALCOHOLIC MYOPATHY

#### 7.3.1. Acute alcoholic myopathy

Acute alcoholic myopathy can develop after several days of heavy binge drinking (Diamond & Messing, 1994) or may occur in chronic alcoholics after a period of particularly high intake. Repeated ethanol administration to human volunteers for 28 days caused muscle damage despite adequate nutrition (Song & Rubin, 1972). The acute syndrome is characterized by localized or generalized muscular aching and tenderness (Hewitt & Winter, 1995), which is often accompanied by muscle cramps. Weakness is present, but may be difficult to demonstrate because of pain; other features include edema of the muscles and subcutaneous tissues. Massive rhabdomyolysis causes metabolic acidosis and hyperkalemia and can produce myoglobinuria, acute renal failure, and disseminated intravascular coagulation (Diamond & Messing, 1994; Hewitt & Winter, 1995; Preedy & Peters, 1994). The development of a complicating compartment syndrome may be delayed for several days after the initial insult to muscle (Hewitt & Winter, 1995). Recovery of acute myopathy usually occurs within days to weeks of abstinence, but residual weakness in proximal muscles may remain (Diamond & Messing, 1994).

#### 7.3.2. Chronic alcoholic myopathy

The chronic syndrome affects 40–60% of alcoholics (Preedy et al, 2003) and is clinically characterized by muscular weakness and wasting (Diamond & Messing, 1994; Slavin et al, 1983), either diffuse, or localized to proximal muscles especially of the pelvic girdle and thighs (Preedy & Peters, 1994). Other common presenting features are frequent falls, difficulties in gait, and muscle cramps. Sometimes pain or tenderness of the proximal muscles occurs (Slavin et al, 1983).

Histologically a decreased diameter of type II muscle fibers (i.e., fast twitch fibers with predominantly anaerobic glycolytic metabolism) is observed. Type IIb fibers, which have no or scarce mitochondria, were more affected than the type IIa fibers (Preedy & Peters, 1994; Slavin et al, 1983). The ultrastructural changes in muscle fibers included intracellular edema, enlarged and distorted mitochondria, dilatation of sarcoplasmic reticulum, excess of glycogen, and lipid deposits containing triglyceride subjacent to the cell membrane and between muscle fibers (Slavin et al, 1983).

In contrast, the mitochondrial-rich type I fibers (i.e., slow twitch fibers with aerobic or oxidative metabolism) are less sensitive and, at least in the early stages, show a compensatory hypertrophy (Trounce et al, 1987). Atrophy of type I and type IIa fibers, which also use aerobic mitochondrial respiration, only occurred in the most severe cases and to a lesser degree (Slavin et al, 1983). In some patients muscle biopsies are normal or show minimal changes. Fiber necrosis or inflammatory cellular infiltration is not seen.

Improvement of chronic myopathy usually takes at least 2–3 months (Diamond & Messing, 1994) up to 6–9 months after abstinence (Preedy & Peters, 1994; Slavin et al, 1983).

### 7.3.3. Mechanisms in chronic alcoholic myopathy

Patients drinking more than 80–100 g alcohol/day for longer than three years may develop muscle atrophy (Slavin et al, 1983). When ethanol becomes the main source of energy, the low protein content of alcoholic beverages may lead to nitrogen malnutrition, as reflected by low serum urea nitrogen levels. In chronic alcoholism protein breakdown exceeded the rate of muscle protein synthesis (Lang et al, 2005), thus compromising the sources of muscle protein and inducing loss of muscle mass.

Further details on the biochemical mechanisms in disturbances of protein metabolism were described in a review by Preedy et al (2001). Evidence for increased oxidative stress by free radicals in alcohol-exposed skeletal muscle was inconsistent (Preedy et al, 1999; 2002).<sup>23, 24</sup>

The predominant atrophy of type IIb fibers suggests that an alcohol-induced effect on carbohydrate metabolism in muscle fibers plays a role (Diamond & Messing, 1994; Slavin et al, 1983). However, the glycolytic pathway tends to be reduced in a variety of myopathies (Preedy et al, 1999) and not exclusively in relationship with alcohol abuse.

Several studies of electrolytes in muscles of chronic alcoholic patients and in alcohol-fed animals showed depletion of electrolytes such as magnesium, potassium, and phosphate (Flink, 1980). Chronic phosphate deficiency has been known to cause subclinical myopathy, and acute hypophosphatemia can lead to proximal myopathy, generalized weakness, and rhabdomyolysis (Berkelhammer & Bear, 1984). Hypokalemia is common in chronic alcoholism and may be associated with myopathy, but its role in the development of alcoholic myopathy is uncertain (Flink, 1980). Hypokalemia, decreased intracellular potassium content, and renal potassium wasting are frequently found in magnesium deficiency. Impaired activity of Na/K-ATPase induced by hypomagnesemia

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23 Although various studies presented molecular and cellular events in alcohol-induced muscle disease, the mechanism of how alcohol produces chronic myopathy remains elusive. A recent review focused on the etiology by which alcohol perturbs the skeletal muscle protein balance and thereby over time produces muscle wasting and weakness (Steiner & Lang, 2015).

24 Does zinc deficiency play a role in the oxidative stress in alcoholic myopathy? In a rodent model of alcoholic myopathy, muscle atrophy was mainly due to alcohol and protein malnutrition. Muscle atrophy was associated with increased lipid peroxidation; either with or without zinc supplementation, in form of zinc sulphate (Durán Castellón et al, 2005). In comparison, low zinc concentrations were associated with oxidative damage and inflammation in other conditions, e.g., critically ill patients with sepsis (Mertens et al, 2015).

would be the cause of these disturbances (Pitts & van Thiel, 1986). Clinically, restoration of potassium cannot be accomplished unless the magnesium deficiency is also corrected (Pall et al, 1987). Furthermore, magnesium deficiency may cause a state of hypocalcemia due to hypoparathyroidism that is resistant to the action of vitamin D or calcium supplements even in substantial doses (Pall et al, 1987; Pitts & van Thiel, 1986). Under these circumstances, supplementation with magnesium corrects the hypocalcemia without the need for calcium supplementation (Pall et al, 1987).

Earlier literature mentioned that features of muscle atrophy in alcoholism would be caused by alcoholic polyneuropathy (Mills et al, 1986), but alternatively coexistent peripheral neuropathy may contribute to muscle atrophy, without a direct causal relation (Diamond & Messing, 1994).

Previous reviews of alcoholic myopathy suggested that muscular atrophy in alcoholics was not primarily related to the patient's nutritional status, or deficiencies of one or more of B vitamins (Preedy & Peters, 1994).

#### **7.4. ALCOHOLISM AND IMPAIRED VITAMIN D STATUS**

The low serum 25(OH)D concentrations in alcoholic patients were discussed by Pitts and van Thiel (1986), describing 14 studies concerning 215 alcoholic patients. Mean serum 25(OH)D levels of 40 nmol/L were found in cirrhotic alcoholics, and 62 nmol/L in non-cirrhotic alcoholics. In the general population, the prevalence of serum 25(OH)D concentrations below 25 nmol/L, ranged from 7.9% [95%-CI: 7.3–8.5] to 16.4% [95%-CI: 15.3–17.5] in two different cohorts of 7,437 persons with a mean age of 45 year (Hypönen & Power, 2007), and of 4,030 persons aged 18–79 year (Hintzpeter et al, 2008). Studies presenting more detailed data on the prevalence of vitamin D deficiency in alcoholic patients are summarized in Table 7–1. In a group of 89 cirrhotic alcoholics, 55% [95%-CI: 45–65] of all patients had 25(OH)D concentrations below 25 nmol/L (Malham et al 2011). In a recent cohort of 21 male alcoholics living in municipal homeless shelters, we found a mean 25(OH)D concentration of 27.9 nmol/L and a median concentration of 17 nmol/L at baseline. Of these alcoholics, 17/21 (81%) [95%-CI: 64–97] had concentrations below 25 nmol/L, and 8/21 (38%) [95%-CI: 18–58] had concentrations below 12.5 nmol/L, indicating severe vitamin D deficiency (Nieuwenhuis, unpublished data).

**Table 7–1.** Prevalence of vitamin D deficiency in alcoholic patients

Studies	Malham et al, 2011	Bang et al, 2009	Kim et al, 2003	Bjørneboe et al, 1986	Hyppönen et al, 2010	Abnet et al, 2010
Nº of alcoholic patients	89	13	18	12	N/A	N/A
Details	Cirrhotic patients	N/A	N/A	Vitamin D intake <sup>a</sup>	General population	General population
Alcohol abuse	Unspecified	Unspecified	Mean 98 g/day <sup>b</sup>	Unspecified	>21 drinks/wk	>14g/day <sup>b</sup>
Mean or median 25(OH)D (nmol/L)	Median 24	Mean 31	Median 54	Mean 56	N/A	N/A
25(OH)D <25 <sup>c</sup> or <30 <sup>d</sup> nmol/L, Nº of patients (%)	49/89 (55%) <sup>c</sup>	5/13 <sup>d</sup>	3/18 <sup>c</sup>	None	63/590 (10.7%) <sup>a,c</sup>	122/512 (23.8%) <sup>a,c</sup>
25(OH)D <12.5 nmol/L <sup>e</sup> , Nº of patients (%)	16/89 (18%)	4/13	N/A	None	N/A	N/A

<sup>a</sup> Not significantly different from controls or non-drinker. <sup>b</sup> One alcoholic drink is 8–14 g ethanol. <sup>c</sup> 25(OH)D <25 nmol/L, vitamin D deficiency. <sup>d</sup> 25(OH) <30 nmol/L. <sup>e</sup> 25(OH)D <12.5 nmol/L, severe vitamin D deficiency. N/A, No further details.

## 7.5. HYPOVITAMINOSIS D MYOPATHY

### 7.5.1. Previous literature

Early clinical descriptions of a myopathy associated with severe vitamin D deficiency recognized a potential association between vitamin D and muscles (Ceglia, 2009). Myopathy has been described in severe vitamin D deficiency responsible for rickets in children and osteomalacia in adults. Traditionally, it was felt that this myopathic presentation was secondary to osteomalacia and inactivity, rather than a direct effect of vitamin D on muscles (Hamilton, 2010). The direct association between vitamin D deficiency and myopathy was based on findings of vitamin D receptors (VDR) present in human muscle tissue (Bischoff et al, 2001), and by VDR knockout mice (Endo et al, 2003). Biopsies of skeletal muscle in adults with vitamin D deficiency have shown predominantly muscle fiber atrophy of the fast twitch type II fibers (Boland, 1986), fibrosis, enlarged interfibrillar spaces and infiltration of fat, and glycogen granules (Yoshikawa et al, 1979), with no signs of inflammatory reactions. Vitamin D supplementation restored muscle tissue (Annweiler et al, 2010) and was associated with an increase of mean diameter and percentages of type II fibers (Ceglia, 2009).

VDR null mutant mice (Bouillon et al, 2008) show growth retardation, osteomalacia, diffuse muscle fiber loss (differing from the human hypovitaminosis D myopathy with a predominance of type II fiber loss), and metabolic changes such as secondary hyperparathyroidism and hypocalcemia (Ceglia, 2009).

### 7.5.2. Clinical findings

Myopathy associated with vitamin D deficient osteomalacia is presenting predominantly as a proximal muscle weakness, muscle wasting, and difficulty in walking upstairs (Hamilton, 2010). Apart from severe cases, hypovitaminosis D myopathy is generally underdiagnosed because of the non-specific symptoms and signs (Annweiler et al, 2010). The first observed symptoms often are muscle weakness and musculoskeletal pain. Generally, the pain is symmetrical and starts in the lower back then spreads to the pelvis, upper legs, and ribs. It is felt mainly in the bones; not in the joints (de Torrenté de la Jara et al, 2004). Muscle weakness can exist during deficiency without biochemical signs of bone involvement (Glerup et al, 2000). The course of myopathic symptoms varied, usually improving within three months (de Torrenté de la Jara et al, 2004), or lasting six to twelve months (Annweiler et al, 2010), mainly depending upon baseline serum 25(OH)D levels and dosage of subsequent vitamin D treatment.

### 7.5.3. Vitamin D deficiency

Normal serum 25(OH)D levels proved to be necessary for maintaining adequate muscle function in a group of 55 vitamin D-deficient women (Glerup et al, 2000). Serum 25(OH)D concentrations below 50 nmol/L were associated with poorer physical performance in 1,234 persons aged 65 year and older in the Longitudinal Aging Study Amsterdam (Wicherts et al, 2007), and concentrations below 25 nmol/L were associated with an increased risk of falling in the same study.

The required serum 25(OH)D concentration is defined by the Institute of Medicine (IOM) as higher than 50 nmol/L (Ross et al, 2011). Others have defined the optimal serum 25(OH)D concentration as  $\geq 75$  nmol/L (Sievenpiper et al, 2008). Even though a traditional reference range of mean  $\pm$  two standard deviations is difficult to determine, because serum 25(OH)D varies with season and geography, concentrations below 20 nmol/L indicated severe deficiency (Compston, 1998; de Torrenté de la Jara et al, 2004). To prevent increased bone turnover, serum 25(OH)D should be higher than 40 nmol/L according to Kuchuk et al (2009), whereas physical performance increased up to 25(OH)D levels of 60 nmol/L in the Longitudinal Aging Study Amsterdam including 1,319 persons aged 65 or older. Concentrations of at least 50 nmol/L were needed to prevent secondary hyperparathyroidism and low bone mineral density in other studies (Malabanan et al, 1998).

Various authors recommend a daily vitamin D intake of 800–1,000 IU (50–62.5 nmol; 20–25  $\mu$ g) for benefits in health (Compston, 1998; Vieth, 1999). The report on dietary requirements for calcium and vitamin D from the Institute of Medicine recommends 600 IU/day of vitamin D for adults, and 800 IU/dag for  $> 70$  years old persons, corresponding to a serum 25(OH)D concentration of at least 50 nmol/L based on the requirements for bone health in  $\geq 97.5\%$  of the population (Ross et al, 2011; [www.iom.edu](http://www.iom.edu)).

#### 7.5.4. Mechanisms in vitamin D-related myopathy

The etiology of the myopathy is multifactorial and attributed to secondary hyperparathyroidism, hypocalcemia, hypophosphatemia, and vitamin D deficiency itself (Holick, 2006; Pfeifer et al, 2002). Studies in rodents have demonstrated that parathyroid hormone induces muscle catabolism (Garber, 1983), and reduces calcium transport, intracellular phosphate, creatinine phosphokinase, mitochondrial oxygen consumption and oxidation of long-chain fatty acids in skeletal muscles (Annweiler et al, 2010).

Research on the vitamin D receptor (VDR) suggested the existence of lower muscle strength in different single nucleotide polymorphisms of the VDR gene and differences of responders and non-responders to vitamin D (Annweiler et al, 2010). The biologically active form of vitamin D, 1,25-dihydroxyvitamin D ( $1,25(\text{OH})_2\text{D}$ ) is critical for the regulation of calcium and phosphate levels that in turn support mineralization and neuromuscular activity (Wang & DeLuca, 2011). In addition to the nuclear  $1,25(\text{OH})_2\text{D}$  receptor (VDR), a less clearly defined cell membrane receptor has been reported (Ceglia, 2009) that mediates the rapid non-genomic actions. The genomic pathway of vitamin D action in muscle involves genomic control (Ceglia, 2009) to regulate the synthesis of proteins responsible for multiple phenomena such as calcium influx into the cell (de Boland & Boland, 1985), membrane phosphate transport, phospholipids metabolism (Drittanti et al, 1988), and muscle fiber proliferation and differentiation (Wu et al, 2000). Rapid responses to  $1,25(\text{OH})_2\text{D}$  are mediated by a membrane-bound vitamin D receptor, through second-messenger pathways that influence calcium transport and regulate intracellular calcium (Ceglia, 2008). According to other investigations, however, identification of tissues expressing VDR has been controversial (Wang et al, 2010) due to false-positive results in detecting specific vitamin D receptors in muscle tissue. Wang & DeLuca (2011) therefore suggested that underlying mechanisms of vitamin D action in muscles are either of an indirect nature or do not involve the known receptor.

Finally, vitamin D may act on the peripheral nervous system, since a reduction of nerve conduction velocity has been reported in cases of severe vitamin D insufficiency (Skaria et al, 1975).

### 7.6. VITAMIN D AND CHRONIC ALCOHOLIC MYOPATHY

#### 7.6.1. Vitamin D, alcoholism, and myopathy

Although alcoholics in the general population may have normal serum  $25(\text{OH})\text{D}$  concentrations (Abnet et al, 2010; Hyppönen et al, 2010), in clinical and outpatient ambulatory settings the majority had subnormal levels even in the absence of active liver disease (Bang et al, 2009; Pitts & van Thiel, 1986). Articles specifically addressing vitamin D in relation to myopathy in alcoholism are rare. Previous studies suggested that changes

in alcoholic muscle disease were not due to dietary deficiencies, but effects of severe vitamin D deficiency in alcoholic myopathy have not been extensively examined. Low 1,25-dihydroxyvitamin D ( $1,25(\text{OH})_2\text{D}$ ) levels were related to reduced handgrip strength and reduced lean mass in a study performed on 90 alcoholics (González-Reimers et al, 2011). Hickish et al (1989) concluded that muscle weakness in 41 male alcoholics was not significantly related to vitamin D deficiency. For serum 25(OH)D concentrations, which had a highly skewed distribution, a transformation of data was used in statistical analysis. However, in smaller patient groups 25(OH)D distributions frequently appeared right-skewed, corresponding with fewer high values in the right tail of the distribution (Figure 7–1) and median < mean values.

Serum 25(OH)D concentrations were below 12.5 nmol/L and maximum voluntary contractions (MVC) of the dominant quadriceps ranging from 70–390 newtons (N) in 10/41 (24%) of the alcoholic patients. The quadriceps MVC of controls ranged from 310–800 newtons (Hickish et al, 1989).

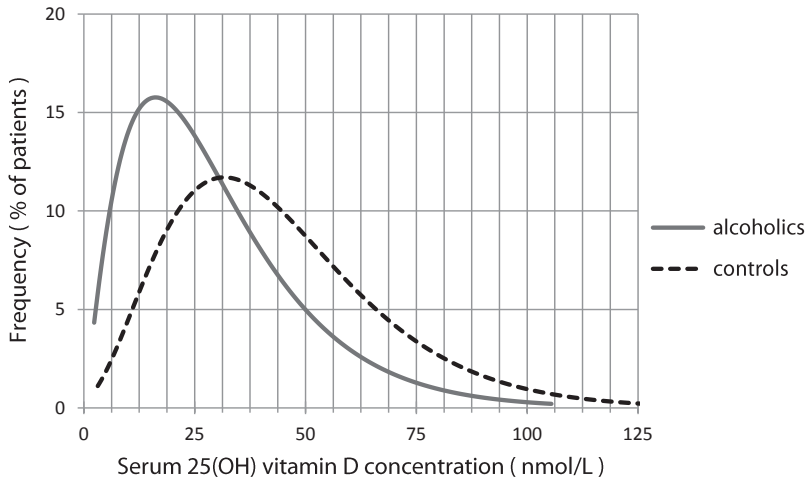
The causes of 25(OH)D deficiencies in alcoholics may include reduced hepatic 25-hydroxylase activity, lack of sun exposure, inadequate dietary intake, and malabsorption. Low vitamin D activity may contribute significantly to the calcium and phosphate deficiencies observed in chronic alcoholism. In a female rat model, Shankar et al (2008) showed that there was a reduction in  $1,25(\text{OH})_2\text{D}$  due altered metabolism in possible relation with ethanol-induced oxidative damage. Alcohol-related osteoporosis responded well to vitamin D therapy (Pitts & van Thiel, 1986). Likewise, chronic alcoholic myopathy might be treated by vitamin D therapy, but a clear understanding of the exact role of vitamin D in alcoholic myopathy is currently lacking. Vitamin D appears to be important for normal skeletal muscle development and optimal muscle strength (Pfeifer et al, 2002), and this may imply a protective role of vitamin D in alcoholic myopathy (cf., vitamin D and nervous system (Annweiler et al, 2010)).

### 7.6.2. Overlap and difference

Similarities between hypovitaminosis D myopathy and chronic alcoholic myopathy were found in:

- (i) clinical descriptions of predominantly proximal myopathy,
- (ii) morphological descriptions of muscle fiber atrophy, lower protein content, and accumulation of glycogen and lipid deposits, and
- (iii) were also found in suggested pathological mechanisms comprising free radicals or muscle antioxidant enzymes.

Finally, (iv) in both conditions comorbidity of polyneuropathy was observed.



**Figure 7–1.** Distribution of vitamin D status in alcoholics and controls

Example of right-skewed distribution of vitamin D concentrations in 74 alcoholic patients (pooled data from: Bjørneboe et al, 1986; Hickish et al, 1989; Nieuwenhuis), and 1,066 controls: median age 61 year, male 73% / female 27%, serum 25(OH)D concentration median 39.1 nmol/L, interquartile range 25.8–56.7 nmol/L, season of blood draw: winter 52% / summer 48% (Abnet et al, 2010). Areas under curves represent 100% of cases. Lowest serum 25(OH)D concentrations are unspecified <7 nmol/L.

Similarities between hypovitaminosis D myopathy and alcoholic myopathy suggest an association between the two, but this does not prove a causal relationship of vitamin D deficiency in alcoholic myopathy. The association of vitamin D deficiency and alcoholism with type II fiber atrophy may be non-specifically related to a similar final pathway of disease occurring in various metabolic myopathies (Slavin et al, 1983).

Differences between hypovitaminosis D myopathy and chronic alcoholic myopathy were found in multiple deficiencies in alcoholic myopathy, such as magnesium, phosphate and thiamine deficiencies. Given the strong interdependency of suboptimal levels of vitamin D, phosphate, and magnesium in chronic alcohol abuse, combined deficiencies may possibly interfere with membrane and intracellular metabolic processes in chronic alcohol-related myopathy; however, it is difficult to identify exact mechanisms of action.

## 7.7. CONCLUSION

Vitamin D supplementation may possibly be an effective target in prevention and treatment of alcoholic myopathy. However, the underlying mechanisms remain unclear. Further research is needed to determine if vitamin D supplementation additionally

can improve muscle function in alcoholic myopathy if alcohol is stopped, and if so, to estimate optimal vitamin D dosages for treatment and prevention of alcohol-related myopathy.

# CHAPTER 8

## **Health benefits of a vitamin D supplementation program in alcoholism: open label randomized controlled trial**

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BMC Public Health (submitted)

Study protocol

Key words: Alcoholism, Alcohol-related disorders, Myopathy, Muscle weakness, Vitamin D deficiency, Cholecalciferol, Malnutrition, Medication compliance, Randomized controlled trial

Trial registration: Netherlands Trial Register (NTR), identifier NTR4114

## ABSTRACT

*Background.* Decreased bioavailability of vitamins may be due to inadequate dietary sources, lower intestinal absorption and/ or liver dysfunction. Muscular weakness and wasting is frequently found in chronic alcoholism and might be related to severe vitamin D hypovitaminosis.

*Design, Setting and Participants.* Participants are community-dwelling adults with a history of alcohol use and who are at risk of multiple vitamin deficiencies. Participants with vitamin D deficiencies of  $<50$  nmol/L serum 25-hydroxyvitamin D (25(OH)D) are randomly allocated to one of two different strategies of vitamin D supplementation. The Vitamin D Intensive Outreach (VIDIO) program includes a cholecalciferol loading dose, if applicable, and subsequent bimonthly high-dose cholecalciferol through an outreach approach of the Street Doctor Service in Rotterdam, the Netherlands. Care As Usual (CAU) includes daily prescriptions of cholecalciferol 800 IU, available in combination with calcium carbonate, and depending on medication compliance of the participants. The VIDIO intervention is based upon general principles to enhance medication compliance for successful treatment, disease prevention, and health promotion, by means of a simple medication regime in one-on-one patient contacts.

Primary outcomes are serum 25(OH)D concentrations. Secondary outcomes include the participants' quadriceps maximal voluntary contractions, gait and balance abilities, results of cognitive screening, and a health-related quality of life evaluation. Prevalences of vitamin D and B<sub>1</sub> deficiencies will be described.

*Discussion.* Mediating variables of vitamin D status are identified by assessing baseline characteristics, liver function and other laboratory findings, help-seeking behavior, social support, and service engagement. Comparison between the two strategies of vitamin D therapy and serum 25(OH)D levels provides insight in the effectiveness of the intervention. Progress in muscle strength in the VIDIO intervention reflects an effect of vitamin D. Possible associations between results of cognitive screening and vitamin D or B<sub>1</sub> deficiencies are discussed.

## 8.1. BACKGROUND

### 8.1.1. Vitamin deficiencies

Alcoholics often develop multiple nutritional deficiencies due to inadequate food intake and because alcohol abuse interferes with the absorption and utilization of several key nutrients. The classic signs of vitamin deficiency only occur in states of extreme depletion and are unreliable indicators for early treatment or prophylaxis of alcoholic patients at risk (Thomson, 2000). The potential health consequences from severe vitamin B<sub>1</sub> (thiamine) deficiency are well described in recommendations concerning diagnosis and management of vitamin B<sub>1</sub> deficiency in alcoholism (Thomson et al, 2002; van den Brink & Jansen, 2009). Other common vitamin deficiencies are in vitamins B<sub>6</sub>, folic acid, and vitamin C (Devgun et al, 1981; Glória et al, 1997). Alcohol abuse may also lead to low serum vitamin D concentrations (Bang et al, 2009; Malham et al, 2011), but estimation of deficiency prevalence in alcoholics is strongly dependent on the population selected to participate in a study. In chronic alcohol abuse, alcohol-related muscle weakness is associated with suboptimal levels of serum vitamin D (Glerup et al, 2000; Latham et al, 2003; Wicherts et al, 2007), and possibly phosphate and magnesium (Pall et al, 1987; Pitts & van Thiel, 1986). Reports on vitamin D status in alcohol-related myopathy are, however, scarce and sometimes even contradictory (Hickish et al, 1989).

### 8.1.2. Aim of the study

The aims of this study are to observe the effectiveness of oral vitamin D supplementation on vitamin D status and muscle performance in vitamin D-deficient alcoholics during two different vitamin D treatment strategies (Figure 8–1) including bimonthly dosages (VIDIO) and care according to standard practice (CAU). The VIDIO intervention is based upon general principles to enhance medication compliance for successful treatment, disease prevention, and health promotion, by means of a simple medication regime in one-on-one patient contacts.

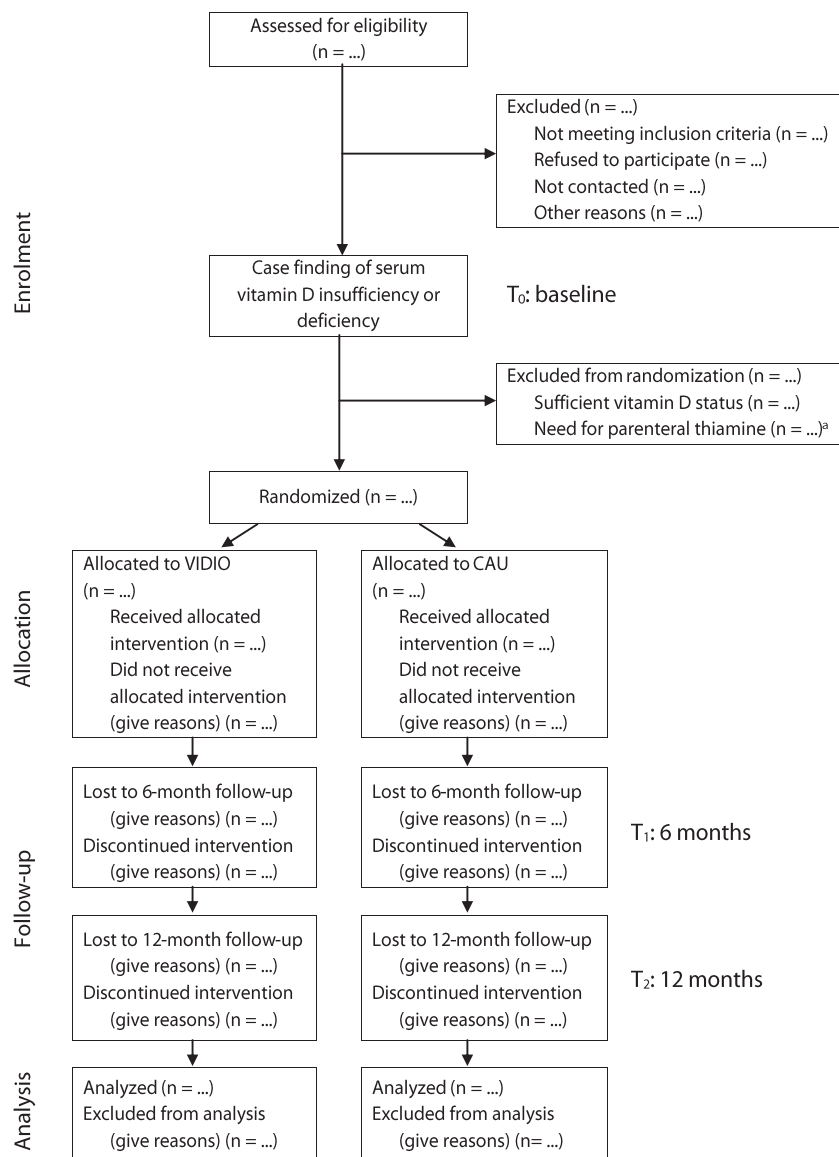
*Hypothesis.* Regarding the aims of the study, it is hypothesized that vitamin D supplementation may be more effective on vitamin D status and muscle performance when given through VIDIO, rather than CAU depending upon medication prescriptions and medication compliance of the participants.

## 8.2. METHOD

### 8.2.1. Design

This is a randomized controlled trial using two different vitamin D treatment strategies in participants with vitamin D deficiencies of < 50 nmol/L serum 25-hydroxyvitamin D

(25(OH)D) and a history of alcohol use. Blood tests are done before vitamin D therapy is started.



**Figure 8–1.** Flow diagram of subject progress through the phases of the study

VIDIO, Vitamin D Intensive Outreach. CAU, Care As Usual. <sup>a</sup> Immediate initiation of parenteral vitamin B<sub>1</sub> (thiamine) treatment is advised in cases as a high risk or serious suspicion of Wernicke encephalopathy has been identified.

Group 1. VIDIO intervention. This group consists of vitamin D-deficient participants who are treated with (bimonthly) high-dose oral cholecalciferol for 12 months, after an initial loading dose according to Table 8–1. They are assigned to two members of the Street Doctor team of the Rotterdam-Rijnmond Public Health Service (GGD, [www.ggdrotterdamrijnmond.nl](http://www.ggdrotterdamrijnmond.nl)). Both professionals, registered nurse and elderly care physician (KGN), are experienced workers in providing primary health care to marginalized people in municipal homeless shelters in Rotterdam since 2001.

Group 2. Care As Usual. The participants in this group receive prescriptions of Calci Chew D3 '500/800' tablets (containing 500 mg calcium carbonate and 800 IU cholecalciferol) by the elderly care physician (KGN) of the Street Doctor team.

The concentrations of serum 25(OH)D are defined as insufficient when less than 50 nmol/L (25 nmol/L 25(OH)D = 10 ng/mL), deficient when less than 25 nmol/L, and severely deficient when less than 12.5 nmol/L (Bang et al, 2009).

Primary outcomes are serum 25(OH)D concentrations. Secondary outcomes include the participants' quadriceps maximal voluntary contractions, gait and balance abilities, results of cognitive screening, and a health-related quality of life evaluation.

### 8.2.2. Participants/ Setting

Participants in the study are community-dwelling adult persons with a history of alcohol use and are selected from previous contacts with the Street Doctor Service/ Rotterdam-Rijnmond Public Health Service (GGD), in Rotterdam, the Netherlands. Candidate participants are visited by the Street Doctor and receive information about the research goals and randomized treatments.

Inclusion criteria are having a history of alcohol use and currently living in Rotterdam and vicinity. Exclusion criteria are knee surgery, first year after hip surgery, pregnancy/ lactating or trying to conceive, inability to give informed consent because of mental incapacity, insufficient command of the Dutch language, already having vitamin D prescriptions for treatment of osteoporosis or hypovitaminosis D myopathy, and contraindications of Calci Chew D3 or cholecalciferol (Health Care Insurance Board (CVZ) Netherlands: *Farmacotherapeutic Compass: Medical Pharmacotherapeutic Information*, [www.fk.cvz.nl](http://www.fk.cvz.nl)): hypercalcemia, renal failure (glomerular filtration rate < 30 mL/min per 1.73m<sup>2</sup>), history of sarcoidosis, lymphomas, hyperparathyroidism, nephrolithiasis/ calculuria, and soya or peanut allergy.

### 8.2.3. Procedure

After providing written informed consent, the Street Doctor discusses the further procedure with the participant and collects information in the baseline interview, preferable in the same session. The Street Doctor will notify regular GP of patient's participation in

the study. The blood tests (Table 8–2) are scheduled within two weeks after the baseline interview. Laboratory results are sent to both Street Doctor and GP. In case of serum 25(OH)D concentrations < 50 nmol/L participants are randomized either to VIDIO or CAU (Figure 8–1). GP's are notified of the randomization outcome. Naturally, participation is on a purely voluntary basis. The protocol is not binding, because a clinician may deviate from the content if strictly necessary for the treatment of the patient. Participants receive €10 with every laboratory and muscle strength testing (a total of €60).

#### 8.2.4. Definition of the interventions

##### *Group 1. Vitamin D Intensive Outreach: VIDIO*

Vitamin D-deficient/ insufficient participants ( 25(OH)D < 50 nmol/L ) randomized to VIDIO will be treated with high-dose vitamin D supplementation consisting of a cholecalciferol loading dose, if applicable (see Table 8–1), and subsequent maintenance dose. The cholecalciferol is dispensed as watery solution (cholecalciferol 50,000 IU = 1 mL) according to a formulation of the Dutch Pharmacists Association (van Groningen et al, 2010). A cholecalciferol loading dose of total 2–4 mL is modified from: dose (IU) =  $40 * (75 - \text{serum } 25(\text{OH})\text{D at baseline}) * \text{body weight (kg)}$ . This equation of van Groningen et al (2010) should not be used in subjects weighing > 125 kg and is here truncated to 4 mL = 200,000 IU. Cholecalciferol maintenance doses are 600 IU/kg once a month, based on a further study of de Boer et al (unpublished data) in visitors of the Outpatient Internal Medicine Clinic.

Holick (2007) described maintenance doses of 800–1,000 IU of cholecalciferol per day or 50,000 IU every two weeks or every month for vitamin D inadequacy in adults. Even higher doses may be considered in case of decreased bioavailability, including malabsorption of vitamin D or obesity. Physicians should use these guidelines in combination with their clinical judgment according to the circumstances. For practical reasons, the VIDIO intervention uses bimonthly maintenance doses of 100,000 IU cholecalciferol, rather than 50,000 IU/month. It has been demonstrated that single doses of cholecalciferol 50,000 or 100,000 IU are safe and effective (Ilahi et al, 2008; van Groningen et al, 2010).

##### *Group 2. Care As Usual: CAU*

Vitamin D-deficient/ insufficient participants ( 25(OH)D < 50 nmol/L ) randomized to CAU receive prescriptions of Calci Chew D3 '500/800' tablets (containing 500 mg calcium carbonate and 800 IU cholecalciferol) by the elderly care physician of the Street Doctor team.

**Table 8–1.** Cholecalciferol doses related to participants' weight and baseline serum 25(OH)D

Serum 25(OH)D baseline	Body weight <sup>a</sup>	Cholecalciferol <sup>b</sup> doses (mL) in Month 1–12 <sup>c</sup>					
		Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
<12.5 nmol/L	48–59 kg	<b>1.5 mL<sup>d</sup></b>	<b>1 mL<sup>d</sup></b>	-	1 mL	-	1 mL
	59–70 kg	<b>1.5 mL</b>	<b>1.5 mL</b>	-	1.5 mL	-	1.5 mL
	70–81 kg	<b>2 mL</b>	<b>1.5 mL</b>	-	1.7 mL	-	1.7 mL
	81–93 kg	<b>2 mL</b>	<b>2 mL</b>	-	2 mL	-	2 mL
	93–120 kg <sup>e</sup>	<b>2 mL</b>	<b>2 mL</b>	-	2 mL	-	2 mL
12.5–25 nmol/L	48–59 kg	<b>1 mL</b>	<b>1 mL</b>	-	1 mL	-	1 mL
	59–70 kg	<b>1.5 mL</b>	<b>1 mL</b>	-	1.5 mL	-	1.5 mL
	70–81 kg	<b>1.5 mL</b>	<b>1.5 mL</b>	-	1.7 mL	-	1.7 mL
	81–93 kg	<b>1.5 mL</b>	<b>1.5 mL</b>	-	2 mL	-	2 mL
	93–106 kg	<b>2 mL</b>	<b>1.5 mL</b>	-	2 mL	-	2 mL
	106–120 kg <sup>e</sup>	<b>2 mL</b>	<b>2 mL</b>	-	2 mL	-	2 mL
25–50 nmol/L	48–59 kg	1 mL	-	1 mL	-	1 mL	-
	59–70 kg	1.5 mL	-	1.5 mL	-	1.5 mL	-
	70–81 kg	1.7 mL	-	1.7 mL	-	1.7 mL	-
	81–93 kg	2 mL	-	2 mL	-	2 mL	-
	93–120 kg <sup>e</sup>	2 mL	-	2 mL	-	2 mL	-
<50 nmol/L	<48 kg	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL	0.5 mL

25(OH)D, 25-hydroxyvitamin D. <sup>a</sup> Body weight limits are chosen on weight distribution for Dutch males and females aged 31–60\* (Delft University of Technology: DINED Anthropometric Database, [www.dined.nl](http://www.dined.nl)).

<sup>b</sup> Dutch registered Aqueous: 50,000 IU per mL. <sup>c</sup> Bimonthly maintenance doses: Month 7 & 9 & 11 equal to Month 5; Month 8 & 10 & 12 equal to Month 6; - = None. <sup>d</sup> Bold text = cholecalciferol loading dose of total 2–4 mL. Target 25(OH)D level = 75 nmol/L. <sup>e</sup> Doses calculations >2 mL are truncated to 2 mL.

### 8.2.5. Follow-up

After 6 and 12 months of supplementation, participants in both vitamin D supplementation groups undergo retests, summarized in Table 8–3, and reassessment of alcohol use, medication currently taken concerning (other) vitamin D preparations, various B vitamins, calcium medication, and benzodiazepines. If serum 25(OH)D levels are > 125 nmol/L, cholecalciferol maintenance strategies will be adjusted to half of the dose (e.g., 50,000 IU bimonthly instead of 100,000 IU bimonthly) or will be discontinued in case of 25(OH)D levels > 200 nmol/L. For safety purposes the toxicity level of 375 nmol/L = 150 ng/mL is used (Holick, 2007), although others reported toxicity usually doesn't occur until 25(OH)D > 600 nmol/L (Hathcock et al, 2007).

### 8.2.6. Effect of interventions

In the analysis phase, the following impact evaluations will be made: Firstly, effects of VIDIO will be compared to CAU, regarding restoration of vitamin D deficiencies. The degree of effectiveness of the VIDIO intervention is evaluated by comparing serum 25(OH)

**Table 8–2.** Blood tests at baseline, besides 25-hydroxyvitamin D

Test	Reference ranges <sup>a</sup>	Remarks
Hemoglobin	♂ 8.5–11 mmol/L ♀ 7.5–10 mmol/L	Anemia?
Cell indices: MCV	80–100 fL	Macrocytic anemia?
Trombocytes	150–370 × 10 <sup>9</sup> /L	Trombopenia in alcoholism?
ALT	♂ <45; ♀ <34 U/L	Liver dysfunction?
AST	♂ <35; ♀ <31 U/L	Liver dysfunction?
GGT	♂ <55; ♀ <38 U/L	Liver dysfunction?
Albumin	35–50 g/L	Malnutrition? Liver dysfunction?
CDT	<1.6% <sup>b</sup>	Chronic alcohol abuse?
Vitamin B <sub>1</sub>	70–140 nmol/L	Deficiency?
Vitamin B <sub>2</sub>	200–360 nmol/L	Malnutrition? Myopathy?
Vitamin B <sub>12</sub>	145–637 pmol/L	Malnutrition? Liver dysfunction?
Folic acid	8–28 nmol/L	Malnutrition? Liver dysfunction?
Magnesium	0.70–1.05 mmol/L	Malnutrition?
Phosphate	0.9–1.5 mmol/L	Malnutrition?
CK	♂ <171; ♀ <145 U/L	Acute alcoholic myopathy?
Urea	2.5–7.5 mmol/L	Protein deficiency? Muscle atrophy?
Creatinine	♂ 65–115 µmol/L ♀ 55–90 µmol/L	Renal dysfunction (MDRD <sup>c</sup> )?
Sodium	136–145 mmol/L	Hyponatremia?
Potassium	3.5–5.5 mmol/L	Hypokalemia? Muscle weakness?
Calcium	2.2–2.65 mmol/L	Hypocalcemia?
TSH	0.4–4.3 mU/L	Myopathy? Cognitive impairment?
Glucose	4.0–6.1 mmol/L	Metabolic dysregulation?

MCV, Mean corpuscular erythrocyte volume. ALT, Alanine transaminase. AST, Aspartate transaminase. GGT, Gamma-glutamyl transpeptidase. CDT, Carbohydrate-deficient transferrin. CK, Creatine kinase. TSH, Thyroid-stimulating hormone. Malnutrition: and/ or Malabsorption. <sup>a</sup> Erasmus MC, Rotterdam: Table. Selected Laboratory Tests ([www.erasmusmc.nl/akc/Patientenzorg/Professionals/labgids/3295019/](http://www.erasmusmc.nl/akc/Patientenzorg/Professionals/labgids/3295019/)). <sup>b</sup> Society for Clinical Chemistry and Laboratory Medicine (NVKC) Netherlands ([www.uwbloedserieus.nl/cdt.php](http://www.uwbloedserieus.nl/cdt.php)). <sup>c</sup> MDRD, Modification of Diet in Renal Disease Study equation to estimate glomerular filtration rate (eGFR; Levey et al, 1999).

D levels in VIDIO at T<sub>1</sub> to levels achieved in CAU at T<sub>1</sub> (see Figure 8–1). Secondly, possible beneficial effects of vitamin D on muscle performance are reviewed. Vitamin D action on muscle strength may be shown by differences in the participants' muscle strength at VIDIO T<sub>1</sub> compared to VIDIO T<sub>0</sub>. Improvements in muscle strength in the VIDIO group reflect an effect of vitamin D. Calculations will also be done for the 12-month (T<sub>2</sub>) follow-up period.

**Table 8–3.** Measurements at three research contacts

	Baseline	6 months	12 months
Serum albumin	X	X	X
Vitamin D and B <sub>1</sub>	X	X	X
Serum calcium and phosphate	X	X	X
Serum creatinine	X	X	X
Other blood tests <sup>a</sup>	X		
Medication assessment <sup>b</sup>	X	X	X
Average alcohol use	X	X	X
MVC quadriceps <sup>c</sup>	X	X	X
POMA <sup>c</sup>	X	X	X
EQ-5D <sup>d</sup>	X	X	X
SES <sup>d</sup>	X		
ASR; section Social Support <sup>d</sup>	X		
SSM <sup>d</sup>	X		
MoCA <sup>d</sup>	X	X	X
Nº of direct patient contacts <sup>e</sup>		X	X

MVC, Maximal Voluntary Contraction. POMA, Tinetti Performance Oriented Mobility Assessment. EQ-5D of the EuroQol Group, a standardized instrument for use as a measure of health outcome. SES, Service Engagement Scale. ASR, Adult Self Report scale. SSM, Self-Sufficiency Matrix. MoCA, Montreal Cognitive Assessment. <sup>a</sup> Further details are given in separate Table 8–2. <sup>b</sup> Medication as listed in exclusion criteria and Table 8–4. <sup>c</sup> Tests performed by JWW or physiotherapist. <sup>d</sup> Tests performed by KGN or Registered Nurse. <sup>e</sup> Street Doctor, RN, and GP for the past six months.

### 8.2.7. Dissemination of information

Results of the blood test are sent to both GP and Street Doctor. Allocated vitamin D strategies are known to GP and Street Doctor. All data are included in the electronic record of the study by two members of the research group (JWW, supervised by AIW), except for the allocated vitamin D supplementation strategies (separate files included by AIW).

## 8.3. MEASUREMENTS

### 8.3.1. Baseline variables

Data on age and sex are collected from the patients' records. Symptoms of alcohol abuse or alcohol dependence are classified according to DSM-5 criteria (American Psychiatric Association, 2013, p. 490–491). Furthermore, participants are interviewed about drug use and psychiatric history. Other baseline variables are given in Table 8–4.

### 8.3.2. Primary outcome measure

Primary outcome measures are serum 25(OH)D concentrations.

### 8.3.3. Secondary outcome measures

Secondary outcome measures are maximal voluntary muscle strength of the participants' dominant quadriceps muscle, the participants' gait and balance abilities, and a health-related quality of life evaluation.

### 8.3.4. Tinetti Performance Oriented Mobility Assessment (POMA)

The Tinetti assessment tool is a task-oriented test of 16 items that measures an (older) adult's gait and balance abilities. The Total test score is 28 points composed of Gait score (12 points) and Balance score (16 points). Interpretations of the Total POMA scores are 25–28 points = low fall risk, 19–24 points = medium fall risk, and < 19 points = high fall risk (scores of geriatric patients; Tinetti, 1986).

### 8.3.5. Muscle function tests

Isometric muscle strength measurement is performed with a hand held dynamometer, MicroFET2. Measurements are only performed on the knee extensors (quadriceps muscle) of the dominant leg with the knee in 90° flexion. The dynamometer is placed at the distal tibia just above the ankle. When necessary, stabilization strips are used to control the dynamometer while testing knee extension in stronger persons. Maximal voluntary contraction (MVC) of the quadriceps muscle will be estimated as the best of three measurements given in newtons (Force of 9.8 newtons  $\approx$  Weight of 1 kilogram). In literature reference values of MVC are available, corrected for gender S (0=male, 1=female), age A in years ( $A > 40$ ), and body weight W in kilograms. For the dominant quadriceps muscle reference values of MVC are defined in newtons (N) as  $358.455 - (87.581 * S) - (3.136 * A) + (2.914 * W)$  based on regression equation in 154 patients aged 50–79 years,  $R^2 = 0.63$  (Andrews et al, 1996).

### 8.3.6. Health-related Quality of Life (EQ-5D)

EQ-5D of the EuroQol Group is a standardized instrument for use as a measure of health outcome (Brooks, 1996; The EuroQol Group, 1990) and consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression. Each dimension has three levels: '1 = no problems, 2 = some problems, 3 = extreme problems'. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

**Table 8–4.** Characteristics at baseline in all participants

Measurements	Body weight	Kg
	Body length	M
	BMI <sup>a</sup>	Kg/m <sup>2</sup>
Medication <sup>b</sup>	Calcium supplements, vitamin D,	Dose/day
	B vitamins, thiamine, benzodiazepines	
	Antiepileptic drugs (Phenytoin, Carbamazepine) <sup>c</sup>	
Alcohol use	On average, days/week	Days
	Number of drinks on a typical drinking day	
	Period of alcohol use / abuse	Years
Sun exposure	Outdoor daytime activities	Minutes/week
Self-neglect	Malnutrition	Yes/ no
	Period of malnutrition	Months, years
	Loss of weight <sup>d</sup>	Kg
Complaints	Muscle pain	Yes/ no
	Muscle cramps	Yes/ no
	Deep bone pain	Yes/ no
	Difficulties in raising from a chair	Yes/ no
	Difficulties in climbing a staircase	Yes/ no

<sup>a</sup> BMI, Body Mass Index. <sup>b</sup> Over-The-Counter medication included. <sup>c</sup> Enzyme-inducing antiepileptic drugs affect endogenous biochemical pathways, as bone metabolism and metabolism of vitamin D resulting in reduction of vitamin D levels (Johannessen & Landmark, 2010; Verrotti et al, 2010). <sup>d</sup> Compared to participant's regular weight.

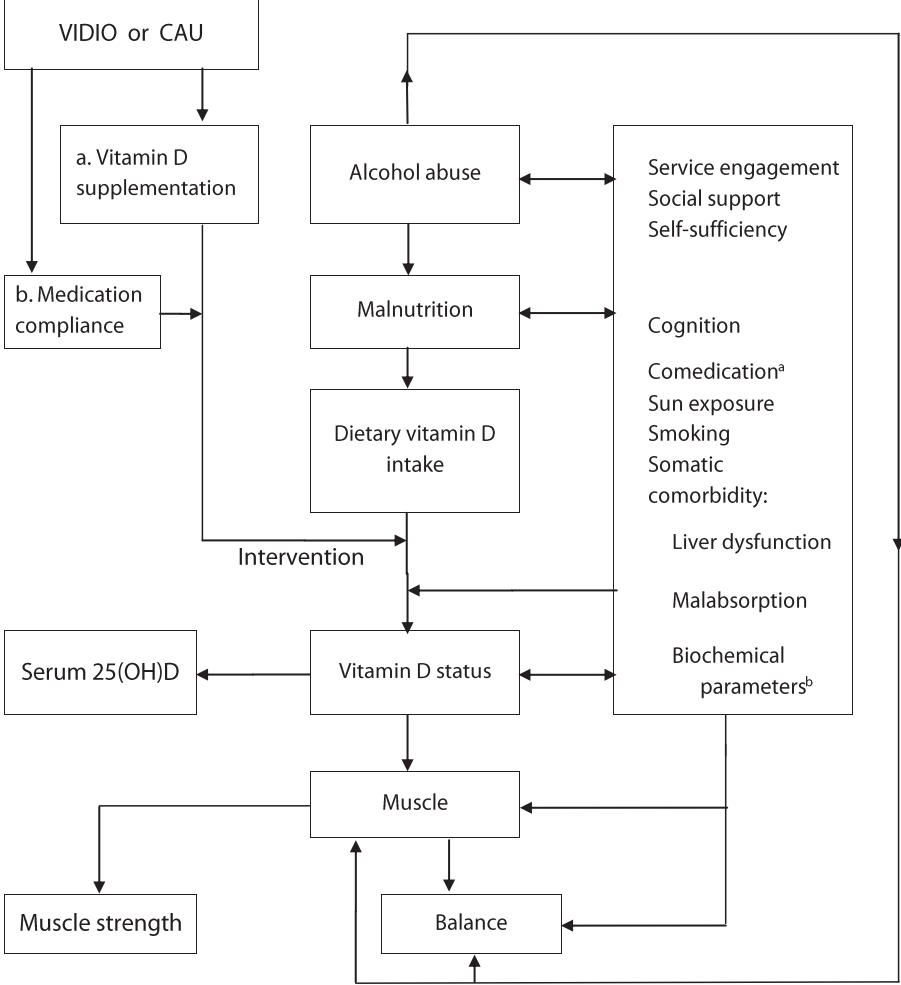
## 8.4. MEDIATOR VARIABLES

### 8.4.1. Characteristics

Age, sex, ethnicity,<sup>25</sup> sunlight exposure (season), education level, weight, body mass index, smoking, level of physical activity, somatic comorbidity, and various biochemical parameters (see Table 8–2) are considered as potential confounders and effect modifiers because these variables may be associated with both vitamin status and muscle strength (Kuchuk et al, 2009).

Level of education is assessed by asking the participant for the highest educational level whether or not completed, classified as primary school, high school, vocational school, college, graduate studies. The level of physical activity (minutes/day) is estimated by assessing household activities, sports, walking outdoors, and bicycling during

25 In keeping with Statistics Netherlands, ethnicity is defined by the parental country of birth; participants with at least one parent born outside the Netherlands are considered to be non-Dutch Statistics Netherlands. Statline; Definitions: Origin, [www.statline.cbs.nl/StatWeb/select ion/?DM=SLen&PA=37325ENG&LA=EN&VW=T](http://www.statline.cbs.nl/StatWeb/select ion/?DM=SLen&PA=37325ENG&LA=EN&VW=T)



**Figure 8–2.** Mediator variables of the effect of vitamin D in alcoholism and self-neglect  
VIDIO, Vitamin D Intensive Outreach. CAU, Care As Usual. 25(OH)D, 25-hydroxyvitamin D. <sup>a</sup> Enzyme-inducing antiepileptic drugs, including hepatic first-pass effects. <sup>b</sup> Biochemical parameters, see Table 8–2.

the previous two weeks (Kuchuk et al, 2009). Cigarette smoking is classified as never, quit, current < 20 cigarettes/day, current ≥ 20 cigarettes/day. Somatic comorbidity is assessed by obtaining a medical history including chronic obstructive pulmonary disease, cardiovascular disease, peripheral arterial disease, stroke, diabetes mellitus, malignant neoplasm, and joint disorders (Kuchuk et al, 2009), without asking for further details.

Other possible mediator variables include the number direct patient contacts, medication compliance, help-seeking behavior, social support, self-sufficiency, cognitive functions, and specific somatic conditions as malnutrition, malabsorption, and liver dysfunction (Figure 8–2).

#### 8.4.2. Laboratory results

Testing serum albumin gives an impression of liver synthesis function in chronic liver disease. Other causes of decreased liver synthesis of albumin are malnutrition and malabsorption. In alcoholism malnutrition, malabsorption, and liver disease may occur in different degrees. Participants are divided in four subgroups by the concentration of serum albumin, including normal serum albumin  $> 35$  g/L, and 'subnormal' 28–35 g/L, 'low' between 21 and 28 g/L, and 'very low'  $\leq 1$  g/L serum albumin concentrations. The limits of 28 g/L and 35 g/L are based on the albumin concentrations of Child-Pugh criteria of severity of liver disease (Child & Turcotte, 1964; Pugh et al, 1973). Other possibly confounding laboratory results in relation to vitamin D and B status are summarized in Table 8–2.

#### 8.4.3. Service engagement (SES)

The Service Engagement Scale is used from the clinician's perspective. The 14 items are rated on a four-point scale 0–3, from 'not at all or rarely' to 'most of the time'. The four subscales refer to availability, collaboration, help seeking and treatment adherence. The English version of the scale has good psychometric properties (Tait et al, 2002).

#### 8.4.4. Social support (ASR)

Social support is measured with the Adult Self Report (ASR) 'social support' scale (Achenbach & Rescorla, 2003). A Dutch translation of the ASR is available. The ASR; section social support includes thirteen items on support by friends or relatives during the past twelve months, from the participant's perspective. Each item is rated on a five point scale 1–5, from 'no help at all' to 'very much help'.

#### 8.4.5. Self-Sufficiency Matrix (SSM)

The Self-Sufficiency Matrix used is adapted from SSM versions of Utah and Arizona<sup>26</sup> and is composed of 11 items selected from original 18 domains: Income, daytime activities, shelter, family relations, mental health, health care, substance abuse, activities of daily living, social support, community involvement, and legal. Each item is rated on a five point scale: '1 = in crisis, 2 = non-self supporting, 3 = limited self-supporting, 4 = sufficiently self-supporting, 5 = fully self-supporting'.<sup>27</sup>

26 SSM version, [www.mnhousing.gov/idc/groups/public/documents/document/mhfa\\_010879.pdf](http://www.mnhousing.gov/idc/groups/public/documents/document/mhfa_010879.pdf)

27 Zelfredzaamheidmatrix, 2013, Lauriks et al, [www.zelfredzaamheidmatrix.nl/LinkClick.aspx?fileticket=1JZyUHDpOQ%3D&tabid=40](http://www.zelfredzaamheidmatrix.nl/LinkClick.aspx?fileticket=1JZyUHDpOQ%3D&tabid=40)

### 8.4.6. Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment is a screening instrument of ten items to assist first-line physicians in detection of cognitive dysfunction, concerning attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. MoCA scores of  $\geq 26/30$  points are considered normal.<sup>28</sup>

## 8.5. FURTHER INFORMATION

### 8.5.1. Randomization

After receiving the baseline laboratory results, an independent Doctor's Assistant allocates participants to one of the two vitamin D supplementation strategies (VIDIO and CAU).

### 8.5.2. Power

To compare differences between both intervention groups in the development of 25(OH)D concentrations in nmol/L and maximal voluntary muscle strength along two follow-up measures, the correlation between repeated measurements must be taken into account (Twisk, 2003). Based on few previous studies (Bang et al, 2009; Hickish et al, 1989), we expect an overall standard deviation in scores of 20 points for 25(OH)D in nmol/L and 112 points for voluntary muscle contraction. Setting an alpha level of 5% and assuming a within-subject correlation coefficient of 0.8, at least 55 patients have to be enrolled to ensure a 80% probability of detecting 50 to 60-point changes in vitamin D concentrations and muscle strength respectively. We have decided to use 80 subjects in each group to make up for those that we anticipate will be lost in follow-up.

### 8.5.3. Statistical analyses

Univariate associations between intervention condition and vitamin D concentrations and voluntary muscle strength are analyzed using standard statistical tests. Longitudinal regression analyses will be performed using mixed models. Interaction effects and collinearities are checked for all significant main factors. Model selection is based on likelihood ratio test statistics. The fit of the final model will be assessed using McFadden R<sup>2</sup> and residual plots. SPSS for Windows is used to perform all statistical procedures.

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28 The Montreal Cognitive Assessment, [www.mocatest.org](http://www.mocatest.org)

#### **8.5.4. Ethical principles**

The study protocol, information brochure and informed consent form were approved by the Erasmus Medical Center ethical committee (registration number NL40553.078.12), and will be performed in accordance with the Helsinki declaration. At this moment the effects of vitamin D supplementation on muscle performance and cognition are unknown and therefore we think it is justified to allocate the participants randomly over the two conditions. The Street Doctor informs the patient of the research aims and randomization method and asks for his or her written informed consent. The patient is free to refuse participation at any time during the research period, without having to disclose a reason why. The collected patient data are treated according to the Medical Confidentiality Rules. Access is limited to members of the research group and the medical ethical committee.

### **8.6. DISCUSSION**

#### **8.6.1. Vitamin D Intensive Outreach**

The choice and design of the interventions is based on an outreach approach in self-neglecting alcoholics. In daily prescribed medications actual intake is not well known, whereas this uncertainty is excluded when providing (bimonthly) supervised doses. Alcohol may have direct toxic effects on muscles, but the relation between muscle weakness and vitamin D deficiency in alcoholism has not been extensively examined. Alcohol-related osteoporosis responded well to vitamin D therapy (Pitts & van Thiel, 1986). A clear understanding of the role of vitamin D in alcoholic myopathy, however, is currently lacking. The central research question in this study is whether either of the two vitamin supplementation strategies can improve muscle performance in hypovitaminosis D-related muscle weakness, as well as vitamin D status in vitamin D-deficient alcoholics.

#### **8.6.2. Muscle strength**

The role of serum 25(OH)D levels in maintaining or improving physical performance and muscle strength is still being discussed. The available studies often vary in their populations studied, severity of baseline vitamin D deficiency, and baseline physical functioning (Lagari et al, 2013). Articles specifically addressing vitamin D in relation to myopathy in alcoholism were scarce (Girgis et al, 2013; González-Reimers et al, 2010). Until now, the effect of vitamin D supplementation on muscle weakness in alcoholic patients is not investigated.

Hickish et al (1989) concluded that maximal voluntary contractions (MVC) of the quadriceps muscle were not significantly related to serum 25(OH)D concentrations in

their study of male alcoholics. The patients were recruited from a Medical Outpatient Clinic. Alcohol abuse was diagnosed on the basis of > 80 g of alcohol consumption daily for more than three years. Of these patients 16/41 (39%) had established liver cirrhosis. The mean age of patients was 43.5 years (range 21–72 years). Vitamin D concentrations were severely deficient and quadriceps MVC varied from 70–390 newtons in 10/41 (24%) of the alcoholic patients, compared to the quadriceps MVC of 310–800 newtons in controls (none of whom drank more than 20 g alcohol daily).

In a group of 55 vitamin D-deficient (non-alcoholic) women, Glerup et al (2000) found that assessment of the serum 25 (OH) D concentrations is a reliable test in the screening for hypovitaminosis D myopathy. The vitamin D-deficient women were treated with a high-dose vitamin D regimen consisting of intramuscular injections of ergocalciferol 100,000 IU per week for one month followed by one injection per month for the following five months; additionally, an oral supplementation of 800–1,200 mg calcium carbonate in combination with 400–600 IU ergocalciferol per day was given. After treatment the most pronounced improvements in muscle strength were seen in the weight-bearing antigravity muscles of the lower limbs (quadriceps muscle). On average, MVC of the quadriceps improved from 259 newtons (66%) at baseline up to 321 newtons (82%) after six months of treatment, compared to the mean quadriceps MVC of 393 newtons (100%) in controls.

Outcomes are dependent on the severity of vitamin D deficiency and substantial dosages in supplementation. Treatment of hypovitaminosis D myopathy may demand high-dose vitamin D treatment for six months or more. When estimating the muscular effects of vitamin D treatment, it is therefore important that the observation period should be at least three months or longer.

### **8.6.3. Cognitive impairment**

Cognitive impairment, whether resulting from or predating vitamin deficiencies, is included as a potential confounder, because of the possibility that cognitive dysfunctioning may be of influence on help-seeking behavior and progression of self-neglect. For older persons, not specifically alcoholics, literature suggests a positive contribution of vitamin D to brain functions (Annweiler et al, 2010). As to mild-to-moderate impairments in intellectual functioning, vitamin D action could play a neuroprotective role in alcohol-related cognitive dysfunctioning (cf. Annweiler et al (2010), vitamin D and nervous system). Furthermore, mild vitamin B<sub>1</sub> deficiencies could be responsible for the mild cognitive limitations and behavioral changes frequently occurring in chronic alcoholic patients – that are commonly attributed to direct toxic effects of alcohol (van den Brink & Jansen, 2009). Cognitive impairment can therefore also be defined as an outcome measure of vitamin depletion. Possible beneficial associations between results

of the cognitive screening and supplementation of vitamin D deficiency or moderate vitamin B<sub>1</sub> deficiencies will be described.

#### **8.6.4. Strengths and limitations**

Important strengths are the clinical relevance and design of this study using reference values of muscle strength based on individual patient characteristics. The participants are visited at home and therefore may represent a more general population of adult patients with alcohol use disorders than a selected group of patients attending ambulatory outpatient care. This is, to our knowledge, the first study which examines the effects of vitamin D supplementation in alcohol-related muscle weakness.

There is some risk that it will not be possible to generalize the results based on the expected response of about 10–20% of the candidate participants. Scores of muscle strength and balance are completed only 2–3 times during the study period rather than more frequently being repeated to observe the amount of intra-individual progress in time. Disadvantages regarding the purpose of a hand held dynamometer are possible stabilization difficulties while testing stronger quadriceps muscles – in which case straps will be used if necessary for stabilization of the device.

Vitamin D supplementation may possibly be an effective target in prevention and treatment of alcohol-related muscle weakness, but in alcoholism the minimal required vitamin D doses are unknown. Very high doses may saturate hydroxylation reactions, thereby reducing the efficiency to generate 25(OH)D within a given period of time (Heaney et al, 2008). Effects of vitamin D supplementation in alcoholism may vary with individual differences in comorbid conditions as malnutrition, malabsorption, and liver dysfunction. Serum 25(OH)D values on average were found to be lower in cirrhotic alcoholics than in non-cirrhotic alcoholics (Pitts & van Thiel, 1986). Determination of dose effect may be uncertain in alcoholic patients suffering from malabsorption and liver cirrhosis. Comedication of calcium supplementation in hypovitaminosis D is not specifically accounted for.

### **COMPETING INTERESTS**

The authors declare that they have no competing interests.

### **AUTHORS' CONTRIBUTIONS**

J.W. Wijnia wrote the manuscript of the study protocol and is the study's principal investigator. A.I. Wierdsma designed the project and helped to draft the manuscript.

E.L. Bresser and E. Oudman helped to define baseline variables. J.P. Wielders supervised information on biochemical tests and vitamin D treatment. A. van de Wiel, O. Breukels, and M.H. Steeghs supervised information on vitamin D treatment. K.G. Nieuwenhuis co-designed the project. A.J. Loonen co-designed the project and supervised information on biochemical tests and vitamin D treatment. C.L. Mulder co-designed and leads the project and led the writing of the manuscript.

# CHAPTER 9

## SUPPLEMENT

### **Cerebellar neurocognition and Korsakoff syndrome: An hypothesis**

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Medical Hypotheses 2010; 75(2):266–268

Key words: Korsakoff syndrome, Cerebellar neurocognition

**ABSTRACT**

In the literature, the cerebellum is given a substantial role in cognitive processes, in addition to traditional views on cerebellar function of regulating motor behavior (Baillieux et al, 2008). The phenomenon of cerebellar damage causing impairments in memory and executive functioning was observed in various cerebellar disorders. Cerebellar cognitive dysfunction can be interpreted as a disturbance of cerebello-cerebral connections to areas of the cerebral cortex involved in cognitive processing, but the exact nature of the cognitive dysregulation is not known.

Memory and executive dysfunction are important clinical features of Korsakoff syndrome. We hypothesize that the Korsakoff syndrome might be an example of cerebellar neurocognitive dysfunctioning (i.e., bilateral crossed cerebello-cerebral diaschisis) caused by neural pathways being disconnected in brainstem areas that are classically affected in Wernicke encephalopathy. Further research is needed to support the possibility of cerebellar neurocognitive disturbances in Korsakoff syndrome. If correct, this hypothesis may contribute to a better understanding of the clinical en neuropsychological profile of Korsakoff syndrome.

## 9.1. INTRODUCTION

Despite substantial knowledge, it has not been yet made clear which defects are particularly responsible for the Korsakoff syndrome, e.g., peri-aqueductal grey matter damage, lesions of the mammillary bodies, the mamillo-thalamic tract, or thalamic nuclei (Kopelman et al, 2009). This uncertainty leaves an opportunity for creating alternative assumptions. Disturbances of executive functioning were customarily regarded as involving the frontal cerebral cortex, but there could be an impact on cortical functioning through disruption of cerebello-cerebral connections (Schmahmann, 2004; Hoppenbrouwers et al, 2008). Thinking about the neuropathologic substrate of the Korsakoff syndrome, we suggest that a bilateral crossed cerebello-cerebral diaschisis (Baillieux et al, 2010) may cause the clinical symptoms of the Korsakoff syndrome.

## 9.2. THE CEREBELLUM AND ITS CONNECTIONS

The traditional view on the functions of the cerebellum consists of regulating motor control. The cerebellum is connected to midbrain, pons, and medulla oblongata by three paired bundles, the superior, middle, and inferior cerebellar peduncles, respectively. These peduncles are among others containing the following tracts: (i) from cerebellum to red nucleus (in the midbrain) and thalamus, (ii) from pontine nuclei to cerebellum, and (iii) from olive (in the medulla oblongata) to cerebellum. Connections between pons and cerebellum, and between olive and cerebellum, are part of cerebellar motor control loops: the connection from the pontine nuclei being 'accelerator', and the connection from the olive being 'brake' of motor movements, to establish smooth and coordinated movements. This regulatory function is applied to intentional movements, e.g., grasping something, as well as to reflex movements, e.g., keeping the eyes focused on a certain point during head movements.<sup>29</sup>

## 9.3. CEREBELLAR NEUROCOGNITION

In the literature is described that the cerebellum would also play an important role in cognitive processing, but this topic inevitably seems to create supporters in favor of this concept and opponents against it (Baillieux et al, 2008). Over the last fifteen years however, the number of disorders (strokes, schizophrenia, pervasive disorders) that are

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29 De Zeeuw, Erasmus MC, Rotterdam, public lecture, October 9, 2009. Brain language: from signal to message.

being associated with cognitive cerebellar functions, has gradually increased (Glickstein & Doron, 2008).<sup>30</sup>

#### 9.4. OWN EXPERIENCE WITH STROKE PATIENTS

As example, we saw three patients during their multidisciplinary stroke rehabilitation, having had acute cognitive impairments following cerebellar stroke, of whom two people with secondary intraventricular hemorrhage.

In these patients, we observed the following non-motor deficits:

(i) symptoms such as disturbances of memory and orientation, analogous with global dementia.

(ii) Furthermore, symptoms that traditionally are interpreted as frontal symptoms, meaning perseveration, impulsivity, disinhibited behavior, and increased distractibility. These symptoms were not present to the same extent in all three patients.

(iii) In one of the patients a marked incoherence of thought was observed.

(iv) Finally, we found symptoms like fatigue, sleeping disorders, depression, or anxiety.

However, the association between structural damage and neurological deficit does not necessarily mean that cerebellar damage was the cause of cognitive dysfunctioning, because hemorrhages may damage neuronal structures or act distantly, e.g., by causing brain displacement.

#### 9.5. CEREBELLAR NEUROCOGNITION IN SUMMARY

Baillieux et al (2008) wrote a review explaining the involvement of the cerebellum in a broad spectrum of cognitive, affective, and linguistic functions: Cerebellar damage would interfere with aspects of memory that rely on executive functions. Priming effects, i.e., quick recognizing and faster response to a known (or similar) stimulus, were not affected in cerebellar lesions. Recognition tasks and the learning of new information the person is not aware of (i.e., implicit learning tasks) remained intact.

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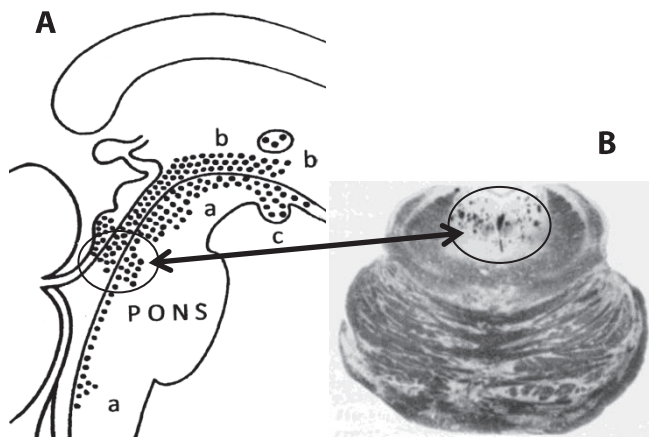
30 Based on research in the field of biological psychiatry, cerebellar abnormalities are considered to play a role in cognitive functioning in schizophrenia – as the cerebellum is engaged in basic cognitive functions such as timing and associative learning (Andreasen & Pierson, 2008).

## 9.6. HYPOTHESIS

We formulate an hypothesis that Korsakoff syndrome might be involving cerebellar neurocognitive dysfunctioning due to disconnection of cerebrocerebellar systems in the classic brain locations of Wernicke encephalopathy (Figure 9–1A and Figure 9–1B). If this hypothesis were to be confirmed, this may provide a better understanding of the clinical profile of Korsakoff syndrome, yet being diagnosed on the basis of an alcohol-related persisting amnestic disorder. In addition, the development and introduction of neuropsychological tests more sensitive to the profile of cerebellar neurocognition in Korsakoff syndrome, might further improve decision-making in clinical diagnosis.

The hypothesis can possibly be tested using MRI techniques to determine structural abnormalities or interruption of neural connections, such as abnormal tissue characteristics in thalamic or brainstem edema, or tissue loss apparent by widening of the aqueduct or enlargement of the third ventricle (Sullivan & Pfefferbaum, 2009). Other MRI techniques could potentially be used to assess disturbances in neural connectivity in these brain regions.

The neural tracts to the cerebellum that might be damaged in Wernicke encephalopathy, are schematically shown in Figure 9–2. The cerebellar superior peduncle, marked by the left white arrow, enters the tegmentum (the roof) of the brainstem and is crossing over to the opposite red nucleus (RN) and thalamus. Furthermore, the olivar route is



**Figure 9–1A.** Localizations of Wernicke encephalopathy. Schematic medial view of distribution of lesions in the brainstem (from a to a; top a is at the level of the midbrain, the upper part of the brainstem), medial thalamus (b) and mammillary bodies (c, convex bulge on both sides of the brain basis (Escourolle & Poirier, 1987, p. 185)).

**Figure 9–1B.** Pinpoint hemorrhages in Wernicke encephalopathy. Microscopic slide with cross section of the pons. There are small black dots (hemorrhages) visible in the upper lighter part of the figure, i.e., the tegmentum (roof) of the pons (Escourolle & Poirier, 1987, p. 184).

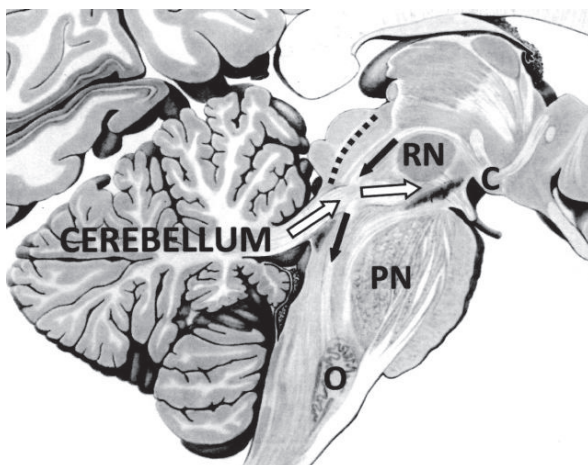
also crossing the tegmentum, shown by the black arrows. We assume that lesions in these pathways may be indicated 'candidate' spots for inducing the Korsakoff syndrome, including the decussating tracts from cerebellum to red nucleus and thalamus.

## 9.7. LIMITATIONS

The hypothesis is based on various information from heterogenic sources: literature on cerebellar neurocognition (Glickstein & Doron, 2008; Hoppenbrouwers et al 2008), personal experience with stroke patients (incomplete and unpublished data), and daily practice of Korsakoff patients (Goossensen et al, 2007). No further theoretical support is yet available, and the concept of cerebellar neurocognition in Korsakoff syndrome has not been previously suggested or described in literature. Further research will be necessary to test this hypothesis.

## 9.8. POSTSCRIPT

Referring directly to our hypothesis, the research group of Pitel reported a diffusion tensor imaging (DTI) study in Korsakoff patients, showing alterations in structural connectivity regarding the fornix and cingulum tracts of the Papez circuit and the superior & middle cerebellar peduncles of the fronto-cerebellar circuit (Segobin et al, 2015). Their data may support the idea of compromised white matter integrity in cerebellar tracts – regarding the superior and middle cerebellar peduncles.

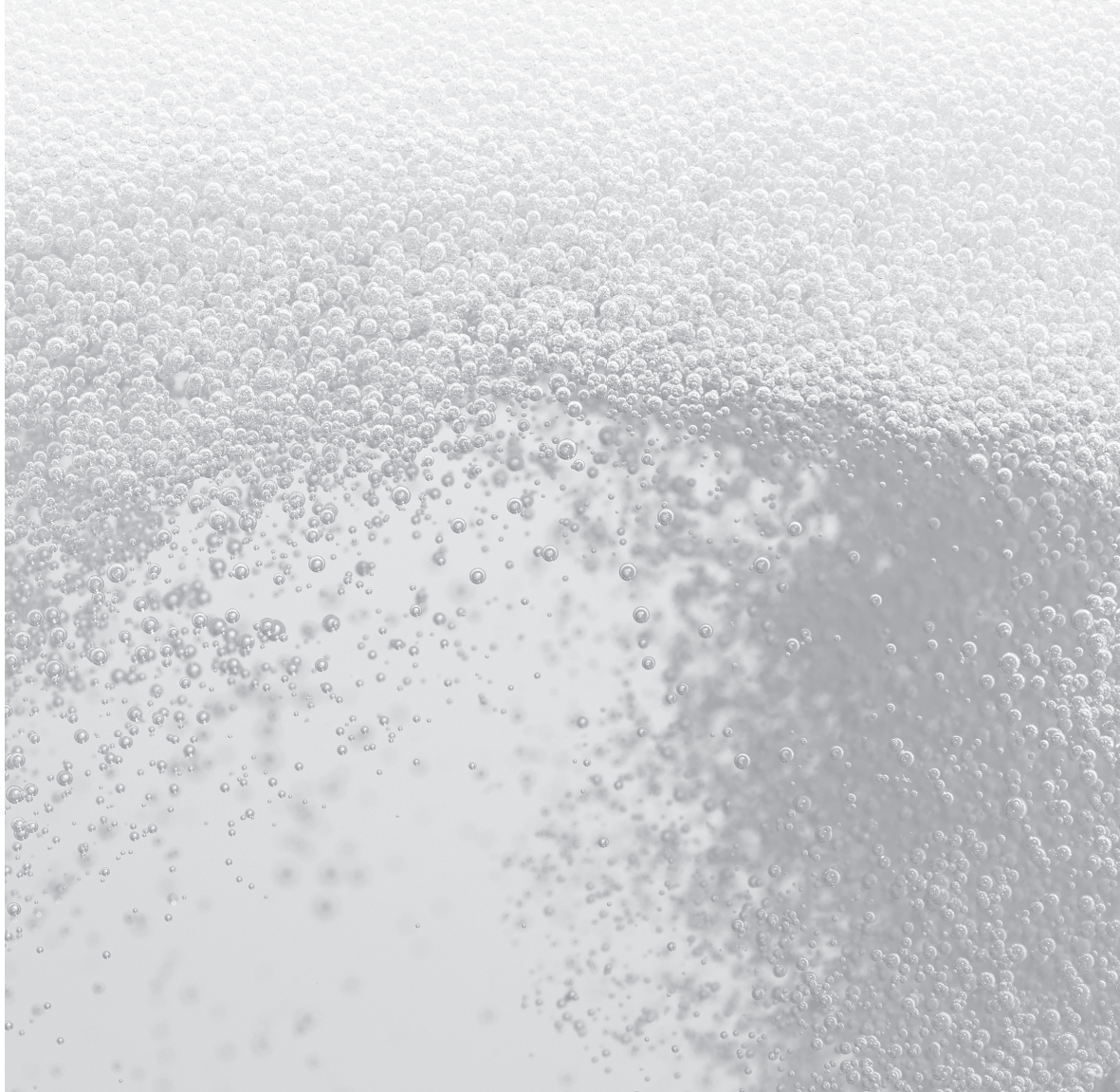


**Figure 9–2.** Neural tracts possibly involved in Korsakoff syndrome. Schematic paramedian view (modified from Nieuwenhuys et al, 1978, p. 53) through cerebellum and brainstem, showing mammillary body (C, corpus mammillare linked to thalamus and midbrain), red nucleus (RN), pontine nuclei (PN) and olive (O). The position of the aqueduct, i.e., the narrow channel connecting the third and fourth ventricle, is indicated by a dotted line.

# **CHAPTER 10**

## **SUPPLEMENT**

### **Thiamine treatment**





### 10.1. CURRENT GUIDELINES

A general review of thiamine treatment dosages is beyond the scope of this thesis, considering the diagnostic approach of the thesis and the availability of extensive guidelines on thiamine treatment in Wernicke-Korsakoff syndrome (Galvin et al, 2010; Thomson et al, 2002; van den Brink & Jansen, 2009). Current treatment guidelines are based on data from uncontrolled trials and from empirical clinical practice. The dose of thiamine required to prevent or treat Wernicke encephalopathy in most alcoholic patients is believed to be 250–500 mg three times daily, given intravenously for 3–5 days (Thomson et al, 2002); or 200 mg three times daily preferably via intravenous instead of intramuscular route, until there is no further improvement in signs and symptoms (Galvin et al, 2010).

### 10.2. INEFFECTIVE TREATMENT

In several cases of Wernicke encephalopathy, no improvement was seen despite early intravenous treatment with high doses of thiamine (Cook et al, 1998). The course of illness may be complicated by serious infections, liver dysfunction, and effects of irreversible thiamine deficiency (Adams & Victor, 1985b). Comorbid deficiencies, such as magnesium deficiency, present another reason why complete recovery may not occur (Dingwall et al, 2015). Remarkably, some of our patients did show clinical improvement on oral thiamine, although orally administered thiamine is generally ineffective in curing Wernicke encephalopathy (Galvin et al, 2010). The reason for this discrepancy is unclear.

### 10.3. LEVEL OF EVIDENCE

In a recent update by the Cochrane collaboration, Day et al (2013) concluded that evidence from randomized controlled clinical trials is insufficient to guide clinicians in determining the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of Wernicke-Korsakoff syndrome. The study of Ambrose et al (2001) met the inclusion criteria provided in the Cochrane Handbook for Systematic Reviews of Interventions, but analysis was limited by methodological shortcomings of the study. Intramuscular thiamine in a dose of 200 mg/day showed significant differences in the patients' responses to a single working memory test (Ambrose et al, 2001), compared with the lowest dose of 5 mg/day.

New controlled trials are unlikely to be undertaken, because of the established cause – i.e., thiamine deficiency – and a high mortality of Wernicke encephalopathy.

#### 10.4. INTRAVENOUS INFUSION OF THIAMINE

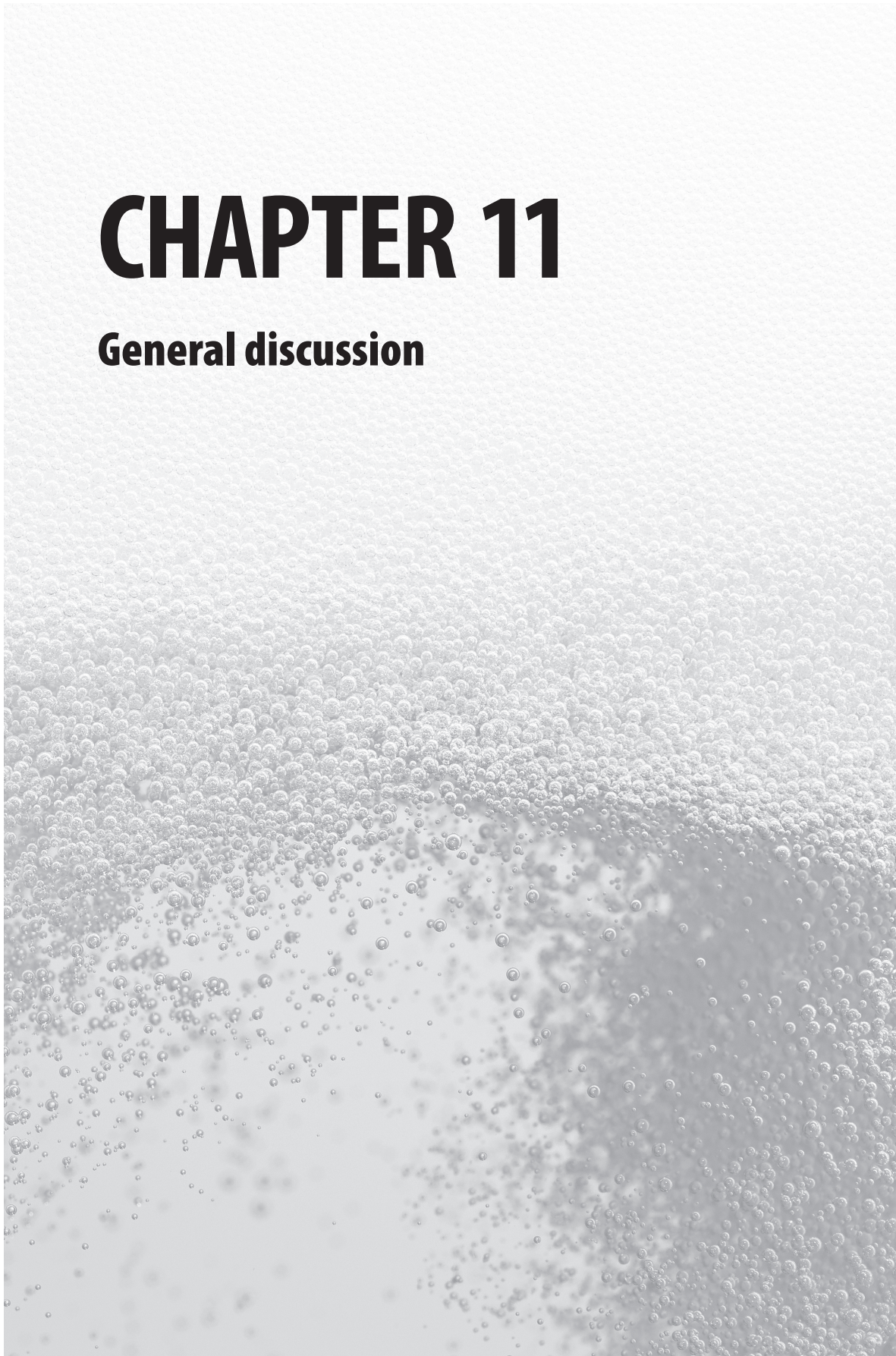
In current practice of referring hospitals in our region we observed that intravenous thiamine was omitted frequently, specialists being cautious with regard to the intravenously (IV) administering of thiamine. However, a more active policy is needed to avoid inadequate treatment in patients who develop Wernicke encephalopathy (Chapter 4, Table 4–4). Therefore, the following practical considerations may possibly encourage a successful uptake of the guidelines on higher dosages of intravenous thiamine in clinical practice. In general the parenterally administering of thiamine is when necessary, safely undertaken in patients without known thiamine hypersensitivity (Arts, 2007; Thomson et al, 2002; Wrenn et al, 1989). Precautions that can be taken are availability of appropriate resuscitation facilities during and after administration, and slow IV infusion: 500 mg thiamine over 30 minutes (Thomson et al, 2002). Thiamine is rarely a cause of anaphylactic reactions<sup>31</sup> (Thomson et al, 2002; Wrenn et al, 1989), but these have incidentally been reported following intravenous (and intramuscular) administering, regardless of previous uncomplicated use (Morinville et al, 1998; Fernandez et al, 1997; Stephen et al, 1992). A possibility is giving a physiological saline IV infusion system and test dosage of 25 mg IM thiamine, followed by infusion of thiamine diluted in normal saline after 15 minutes if no adverse reactions have occurred (Wernicke protocol, Academic Hospital of Maastricht, [www.neuromaas.nl](http://www.neuromaas.nl)), but in case of emergency any delay is undesirable (Thomson et al, 2002).

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31 Life-threatening allergic reactions to any parts in thiamine supplements.

# CHAPTER 11

## General discussion





## 11.1. WERNICKE DELIRIUM

Research question (I): Are Wernicke encephalopathy and delirium synonymous conditions in malnourished alcoholic patients?

### 11.1.1. Introduction

Some authors wondered whether the clinical manifestations of Wernicke-Korsakoff syndrome can mask delirium symptoms (Djelantik et al, 2015), while others suggested that patients were sometimes diagnosed as having delirium tremens instead of Wernicke-Korsakoff syndrome (Cook et al, 1998). In this thesis, we have attempted to systematically examine the clinical significance of delirium in relation to the Wernicke-Korsakoff syndrome and to further explore the link between thiamine deficiency, delirium, and Wernicke-Korsakoff syndrome.

Wernicke encephalopathy can easily be mistaken for alcohol withdrawal delirium (Rosenbaum, 2003). In previous literature, van Epen (1983) emphasized the frequent occurrence of atypical and 'transitional stages' – i.e., the variable clinical course of alcohol-related syndromes in chronic alcoholism, including atypical features, along with well-defined 'classical' syndromes. For example, when a patient is admitted to hospital with an acute alcohol hallucinosis, suffering with a delirium tremens a few days later, and is obviously exhibiting a Korsakoff syndrome after the delirium has resolved (van Epen, 1983). This symptom pattern of a delirium progressing to Korsakoff syndrome was observed in many of our patients.

### 11.1.2. Alcohol withdrawal delirium

In general, a delirium results from structural brain lesions, systemic disease, and either intoxication or withdrawal from pharmacological or toxic agents such as alcohol (Adams & Victor, 1985a, p. 307–308; Kaplan et al, 1994, p. 338–339).

There is little information available regarding the course of alcohol withdrawal syndrome in a general hospital (Monte Secades et al, 2010). Prolonged alcohol withdrawal delirium was described in several case report studies – the patient's course being complicated by somatic comorbidity, failure of benzodiazepine medication to prevent delirium or shorten its duration, and occasionally the onset of Wernicke encephalopathy (Hayes et al, 2007; Lemyze et al, 2009; Miller, 1994; Narumoto et al, 2005). However, we assume that these prolonged and protracted deliria may be a primary manifestation of Wernicke encephalopathy preceding the development of Korsakoff syndrome.

### 11.1.3. Results in support of Wernicke delirium

In an observational study of patients with end-stage Korsakoff syndrome (Chapter 3) we have highlighted that delirium in malnourished alcoholic patients may be considered

to be synonymous with Wernicke encephalopathy. In this study we found support for the hypothesis that delirium in itself can be a primary presenting feature of Wernicke-Korsakoff syndrome in self-neglecting alcoholic patients. During the initial stages of disease, deliria were reported in 35/73 (48%) alcoholic patients with subsequent Korsakoff syndrome (Chapter 3). The patients had multiple potential causes for delirium, e.g., alcohol withdrawal or somatic diseases. However, based on our findings in this study of Korsakoff patients, we suggested that at least 17% (95%-confidence interval: 10–25%) of their delirious conditions in the early stages of Wernicke-Korsakoff syndrome may have occurred due to an unrecognized Wernicke encephalopathy with incomplete presentation.

#### **11.1.4. Pathophysiology of Wernicke delirium**

In a review of pathophysiological mechanisms in delirium (Chapter 5), we further provided arguments in support of a link between thiamine deficiency and delirium. The possible loss-of-function mechanisms following thiamine deficiency in Wernicke-Korsakoff syndrome are proposed to come from microglial activation, resulting in the delirium in the initial phase of the syndrome.

#### **11.1.5. Microglial activity in Wernicke delirium**

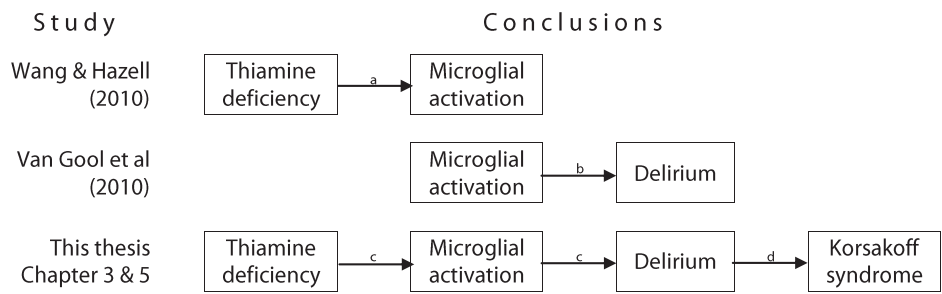
Although delirium is a common disease, the pathophysiology of delirium remains poorly understood, and its underlying mechanisms are largely unknown (Inouye & Ferrucci, 2006). Mechanisms may differ in various clinical settings (Flacker & Lipsitz, 1999).

In inflammatory-associated delirium, literature suggested that the delirium is an immunity-induced dysregulation characterized by metabolic alterations and progressive neuronal loss (Teeling & Perry, 2009). Van Gool et al (2010) described a delirium model on proinflammatory factors released by microglia escaping from cholinergic inhibition. The cascade of cytotoxic reactions that might follow, could account for delirium and damage to the cholinergic neurons.

The study by Wang and Hazell (2010) suggested that microglial activation played a role in the development of neurological impairment in thiamine deficiency and possibly Wernicke encephalopathy. The combining of this information (Figure 11–1) may contribute in favor of the clinical observations that delirium can be seen as an important presenting feature of Wernicke-Korsakoff syndrome and might be one of the key symptoms of an active Wernicke encephalopathy.

#### **11.1.6. Strength and limitations**

We propose a change of viewpoint in the diagnostic and therapeutic approach to Wernicke encephalopathy that recognizes the initial symptoms of thiamine deficiency overlapping with many symptoms of delirium and examines the interrelations between



**Figure 11–1.** Thiamine deficiency, microglia, delirium, and Korsakoff syndrome  
Relationships are displayed by arrows: <sup>a</sup> Association from animal study. <sup>b</sup> Hypothesis (review of literature).  
<sup>c</sup> Suggested possible mechanism. <sup>d</sup> Descriptive, retrospective data.

both delirium and cognitive deficit in Wernicke-Korsakoff syndrome. Based on our findings and review of literature, we more distinctly introduced the entity of ‘Wernicke delirium’ and provided information on its possible mechanisms of action.

The present studies have several limitations. The completed available patients’ information on alcohol withdrawal was small in number (Chapter 3), because it is difficult to obtain a reliable past medical history in non self-sufficient alcoholic patients.

In older people, the risk of delirium was associated with alcohol use (Ahmed et al, 2014; Elie et al, 1998), irrespective of alcohol withdrawal delirium (Robinson et al, 2009). However, in many studies on risk factors of delirium, there were only small numbers of patients ( $\leq 10$ ) in the comparison of delirium and alcohol consumption and essential details of alcohol quantities were frequently lacking.

In our review on delirium-biomarkers (Chapter 5) no descriptions are given of how delirium was assessed in the original studies. From an etiological point of view, it is very unlikely that a single genetic or biochemical marker would account for most of the symptoms in delirious states. Although the biomarkers listed may have an association with delirium, evidence for causality is lacking. The review is based on limited selection criteria regarding the pathophysiology of delirium and may be prone to selection biases lacking data from grey literature or other articles describing loss-of-function mechanism in delirium.

**11.1.7. Conclusion to research question (I)**

Based on the preliminary findings of deliria without any other obvious causes (Chapter 3) we suggest that delirium and Wernicke encephalopathy were synonymous conditions in our selected patient group of self-neglecting alcoholic patients – in whom the Wernicke phase resulted in having Korsakoff syndrome. The diagnostic label of delirium due to thiamine deficiency or ‘Wernicke delirium’ may be the better alternative to achieve

an early detection of Wernicke encephalopathy. Pathophysiological mechanisms of thiamine deficiency delirium were reviewed by combining literature on delirium and literature on thiamine deficiency. We suggested that microglial activation noted in studies of inflammation-related delirium may play a role in the pathogenesis of thiamine deficiency delirium.

#### **11.1.8. Consequences for daily practice**

As mentioned before, a recognized episode of Wernicke encephalopathy is not always obvious. In clinical practice the classical presentation of the triad symptoms is limited and constitutes only 16% of cases (Harper et al, 1986). Unfortunately, delirious states may also go unrecognized because of either a relatively non-specific clinical presentation in some cases or poorly recognized clinical symptoms and signs. Compared with Wernicke's triad symptoms, however, Wernicke delirium may pose a new challenge in the diagnosis of active Wernicke encephalopathy. Thus recognition of Wernicke delirium may be helpful to raise the clinician's index of suspicion about Wernicke-Korsakoff syndrome.

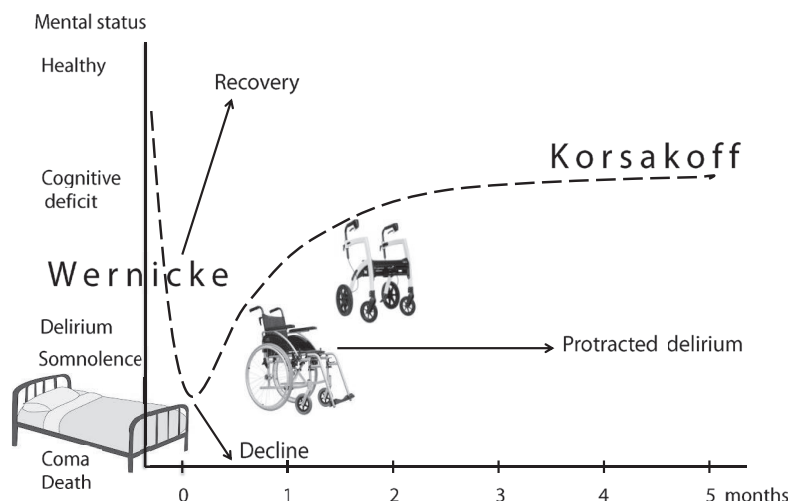
### **11.2. GAIT DISORDER IN WERNICKE DELIRIUM**

Research question (II): Wernicke-Korsakoff syndrome is a 'spectrum of disease' resulting from thiamine deficiency, but would it be possible to more specifically determine its temporal progression regarding the patients' mobility and mental symptoms?

#### **11.2.1. Representative case report**

The Wernicke-Korsakoff syndrome affects both mobility and mental ability. In a detailed case history (Chapter 4) we described the association of gait and balance disorders with mental status changes in the encephalopathic Wernicke phase and subsequent Korsakoff syndrome (Figure 11–2).

"On hospital admission the patient had impaired consciousness, with fluctuating drowsiness. He was bedridden because his poor balance had left him unable to walk. On day 16, he sustained his attention relatively well, but his glazed eyes showed that he was not very alert. He had difficulty organizing his thoughts and he expressed himself incoherently. By now the patient could walk again with a walker and help from one person. During week 15, the patient had a full neuropsychological assessment. Clinically, he showed striking perseverations and confabulations. The assessment revealed disorders in orientation, memory, and executive functions, and was consistent with a developing Korsakoff syndrome. After week 17, he could walk independently without any aids."



**Figure 11–2.** A patient’s mobility and evolving neuropsychiatric symptoms in Wernicke-Korsakoff syndrome (dashed line), starting with initial hospitalization at 0 months. Arrows depict alternative outcomes: further decline, full recovery, or protracted delirium.

### 11.2.2. Gait disorder in alcoholism

Alcohol-related unsteady gait may result from various problems in different parts of the nervous system or of the body. In addition to Wernicke encephalopathy, the more common alcohol-related gait disorders include alcohol intoxication, cerebellar dysfunction, alcoholic polyneuropathy, and alcoholic myopathy, among others.

Purkinje cells of the cerebellum are susceptible to different forms of alcohol-related injury. Alcohol can impair cerebellar function by enhancing  $\gamma$ -aminobutyric acid (GABA)-mediated inhibition of the Purkinje cells, thus depressing Purkinje cell activity. Moreover, alcohol is known for its inhibitory effects on glutamatergic transmission, most obvious for N-methyl-D-aspartate (NMDA) receptors, e.g., in Purkinje cells during development and at climbing fiber synapses onto mature Purkinje cells (Belmeguenai et al, 2008). Other studies described that alcohol directly affects the cerebellum via inhibition of cerebellar granule cells, mediated by extrasynaptic GABA A receptors (Carta et al, 2004; Hancher et al, 2005). The effect of this increased GABA inhibition is impaired motor coordination. Alcohol-induced motor coordination deficits and ataxias are usually reversible, but chronic alcohol abuse may cause cerebellar atrophy with permanent gait ataxia and memory loss – most probably caused by thiamine deficiency, rather than alcohol consumption alone (Harper, 2009).<sup>32</sup>

32 Ataxia; [www.hopkinsmedicine.org/neurology\\_neurosurgery/centers\\_clinics/movement\\_disorders/ataxia/conditions/](http://www.hopkinsmedicine.org/neurology_neurosurgery/centers_clinics/movement_disorders/ataxia/conditions/)

### 11.2.3. Strength and limitations

The temporal progression of Wernicke's symptoms, including (simultaneous) disturbances of gait during follow-up, is seldom described. The combined course of mental and mobility changes in Wernicke-Korsakoff syndrome illustrated in this case report, may be considered exemplary for many Wernicke-Korsakoff syndrome cases – but needs extended descriptive research, regarding the proportions of patients with progression to end-stage Korsakoff syndrome, or other, alternative outcomes, i.e., full recovery, further decline, or persisting delirium (Figure 11–2).

### 11.2.4. Conclusion to research question (II)

The combined progression of a patient's mental and mobility symptoms was shown in a representative case study. It is crucial to attach a lot of importance to impaired gait in malnourished alcoholic patients. If an alcoholic patient is confined to bed because of illness, the impaired mobility should weigh heavily in the decision-making process of early WKS diagnosis and treatment.

### 11.2.5. Other consequences for daily practice

Hypothetically, assessing the final Korsakoff syndrome diagnosis becomes relevant when the patient with suspected Korsakoff syndrome can walk independently (again).

In the described case history, the patient's Wernicke encephalopathy was missed and inadequately treated, being labeled as 'probable Korsakoff syndrome' far too early.

## 11.3. INFECTIONS IN THE WERNICKE PHASE AND COGNITIVE OUTCOMES

Research question (III): How common were infections in the initial phase of Wernicke-Korsakoff syndrome in our patient group?

Research question (IV): Were infection parameters related to the cognitive outcomes?

### 11.3.1. Introduction

Wernicke encephalopathy arises as a result of thiamine deficiency and is most frequently associated with alcohol abuse. However, thiamine deficiency may also occur in clinical scenarios such as severe sepsis, unexplained heart failure or lactic acidosis, starvation, chronic malnutrition, long-term parenteral feeding, hyperemesis gravidarum, or bariatric surgery (Manzanares & Hardy, 2011). In fact, serious infections are common in the initial phase of Wernicke-Korsakoff syndrome (Chapter 6).

Regarding cognitive outcomes, it is already well known that executive dysfunction, as well as memory dysfunction, is an important clinical feature of the Korsakoff syndrome (Kessels et al, 2008; Kopelman et al, 2009; Thomson et al, 2002). Because of the different

aspects of cognitive disturbances, we chose to separately examine the non-memory section of the Cambridge Cognitive Examination (CAMCOG) and the subtests of the Behavioral Assessment of the Dysexecutive Syndrome (BADS), including the 'Key search test' among others.

### **11.3.2. Cognitive outcomes**

The main result of Chapter 6 was to show that infection parameters such as white blood cell (WBC) counts and absolute neutrophil counts (ANCs) in the early stages of Wernicke-Korsakoff syndrome predict poorer long-term outcome in terms of neuropsychological testing. Although most tests showed a negative correlation between white blood cell counts and neuropsychological test scores, correlations were statistically significant in only one or two non-memory tests.

### **11.3.3. Strength and limitations**

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 Wernicke-Korsakoff syndrome.

The present study has several limitations. There were limited data regarding a complete set of relevant parameters of infection. Secondly, possible covariates of white blood cell counts, e.g., smoking, amount of stress, or thiamine deficiency itself, were not taken into account. Furthermore, it is not yet clear to what extent white blood cell counts do reflect the presence of infections in Wernicke-Korsakoff syndrome in those cases where no infections were found.

### **11.3.4. Conclusions to research questions (III) and (IV)**

Severe infections were common during the Wernicke phase of Korsakoff patients admitted to Slingsdael 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 Wernicke-Korsakoff syndrome. Based on current results we suggest that infections may exacerbate the negative impact of thiamine deficits in vulnerable brain areas, but perhaps not quite as much in already severely depleted thiamine reserves.

### **11.3.5. Consequences for daily practice**

The overall message of Chapter 6 is that 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 Wernicke-Korsakoff syndrome is far more commonly reported in the context of alcohol, there is now established evidence for Wernicke-Korsakoff's in malnourished patients without alcohol, such as in anorexia nervosa, hyperemesis gravidarum, post-gastric surgery (Kotha & De Souza, 2013; Milone et al, 2014; Renthall et al, 2014), and in several cases with serious comorbid infections (Chidlovskii et al, 2012; Kishimoto et al, 2012; Schattner & Kedar, 2013).

### 11.3.6. 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 impact of systemic infection on cognitive functioning:

- (i) If indeed there is a correlation between infection and worse outcomes in Wernicke-Korsakoff syndrome, then can it be said that infection itself is linked to a poorer prognosis,
- (ii) or is it that the infection is a marker of more severe degrees of thiamine deficiency?
- (iii) Might there be a bottom effect, since infection will utilize already depleted thiamine stores?
- (iv) Can possible cognitive effects of systemic inflammation in Wernicke-Korsakoff syndrome be interpreted in terms of a differential vulnerability of brain areas involved in executive functioning and those involved in memory function?
- (v) Are worse cognitive outcomes more specifically related to septic conditions or, e.g., endotoxines of gram-negative bacteria? <sup>33</sup>

## 11.4. FURTHER CONSIDERATIONS ON MECHANISMS IN WKS

So far, we have highlighted the linkage between thiamine deficiency and delirium and emphasized the occurrence of coincidental infections and its possible impact on the Wernicke-Korsakoff syndrome. Based on the review of Chapter 5 we suggested that inflammation-related delirium (van Gool et al, 2011) and thiamine deficiency delirium may share comparable underlying mechanisms. Furthermore, in Chapter 6, we hypothesized on associations between the severity of thiamine deficiency, systemic inflammatory processes, and neurocognitive damage in Wernicke-Korsakoff syndrome. However

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33 Endotoxin (lipopolysaccharides): Toxin contained in the cell walls of some micro-organisms, especially gram-negative bacteria, that is released when the bacterium dies and is broken down in the body. Fever, chills, shock, leukopenia, and a variety of other symptoms result, depending on the particular organism and the condition of the infected person (*Mosby's medical dictionary*, 8<sup>th</sup> edition. Elsevier; 2009).

there is no clear understanding of the basic mechanisms by which the overall syndrome occurs (Cf., Hazell & Butterworth, 2009).

The pathogenesis of Wernicke-Korsakoff syndrome may probably consist of different interdependent processes related to inflammatory factors, metabolic effects due to thiamine deficiency, and occasionally comorbid conditions such as magnesium deficiency and diabetes mellitus. For instance, in a postmortem study of Wernicke encephalopathy cases, the neuropathological findings in the thalamus and inferior olivary nuclei were different compared with those of the mammillary bodies and the subependymal structures along the third and fourth ventricles and the aqueduct. In contrast with the latter brain regions, the thalamus and inferior olivary nuclei showed neuronal loss histologically resembling neuronal disintegration as seen in anoxic necrosis (Torvik, 1985).

*Inflammatory mechanisms in thiamine deficiency.* In a recent update Abdou & Hazell (2015) summarized the complex pathophysiologic mechanisms in thiamine deficiency and the role of impaired oxidative metabolism, lactate production of astrocytes, lactic acidosis, increased extracellular glutamate levels, glutamate receptor activation, glutamate-mediated excitotoxicity in glia cells, i.e. astrocytes and microglia, resulting in – or associated with – oxidative stress and inflammatory processes, all features of thiamine deficiency.<sup>34, 35</sup>

*Magnesium deficiency.* Thiamine is an essential co-factor for a number of enzymes involved in carbohydrate metabolism and requires optimal levels of magnesium for biological function. Chronic alcoholic patients are at risk of developing combined deficiencies of thiamine and magnesium (Peake et al, 2013). Furthermore, hypomagnesemia may be a rare but serious complication of proton pump inhibitors in patients concomitantly receiving diuretics (Danziger et al, 2013), e.g., in alcoholic patients suffering of esophagitis, liver cirrhosis, and ascites.

*Diabetes mellitus.* Glucose is the main energy source for the brain. In times of starvation, however, the brain has the capacity to adapt to the use of ketones for its energy requirements. Ketogenesis is normally inhibited by insulin hormone. In low levels of circulating insulin – as seen during starvation and diabetic ketoacidosis – ketones are formed by  $\beta$ -oxidation of free fatty acids in the liver. It appears that astrocytes play a role in regulation of brain energy metabolism and are capable of producing ketones from fatty acids, as well (White & Venkatesh, 2011).

We assume that hyperglycemia in uncontrolled diabetes mellitus may further deplete already marginal thiamine reserves in malnourished alcoholic patients. Further research

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34 Glutamate receptors include among others N-methyl-D-aspartate (NMDA) receptors.

35 Excitotoxicity: Neuronal injury caused by excessive release of excitatory neurotransmitters – glutamate and aspartate, causing damage to nerve and glial cells (Segen JC. *Concise dictionary of modern medicine*. The McGraw-Hill Companies, Inc; 2002).

is necessary to clarify these issues and to determine whether diabetes mellitus could be an additional risk factor in thiamine deficiency.

Clearly, a thorough understanding of the course of Wernicke-Korsakoff syndrome is currently lacking. The associations between the severity of thiamine deficiency, systemic inflammatory processes, and neurocognitive damage in Wernicke-Korsakoff syndrome are complex and need to be tested by additional studies based on different methodological approaches.

## 11.5. ALCOHOLISM, VITAMIN D DEFICIENCY, AND MUSCLE WEAKNESS

Research question (V): Is vitamin D deficiency a confounder in alcoholic muscle weakness?

### 11.5.1. Vitamin D deficiency

The causes of vitamin D deficiency in alcoholism may include liver dysfunction, lack of sun exposure, malabsorption, and inadequate dietary intake. As previous studies suggested that a deficiency in diet could not cause alcoholic muscle disease, our review indicates that vitamin D deficiency might partly explain why myopathy is so often observed in chronic alcoholism.

### 11.5.2. Recent research on vitamin D supplementation

The serum 25(OH)D response to supplementation depends on several factors, e.g., baseline 25(OH)D level, BMI, and genetic factors.<sup>36</sup> However, whether this is clinically important or not depends on the therapeutic window of vitamin D, an issue that is still not settled (Didriksen et al, 2013). Figure 11–3 shows mean 25(OH)D levels at baseline and following different vitamin supplementation regimes in small groups of healthy participants (Ala-Houhala et al, 2012; Close et al, 2013; Diamond et al, 2013; Goswami et al, 2012; Knutsen et al, 2014; Lehmann et al, 2013; Owens et al, 2014; Wicherts et al, 2011) or in selected patient groups with various degrees of vitamin D deficiency (Bogh et al, 2012; Dinizulu et al, 2011; Karaplis et al, 2011; Leidig-Bruckner et al, 2011). In a randomized clinical trial of vitamin D deficiency with baseline serum 25(OH)D levels of < 25 nmol/L and six months follow-up, supplementation with vitamin D in doses of 800 IU/day versus 100,000 IU/3 months gave comparable results, i.e., the mean baseline value

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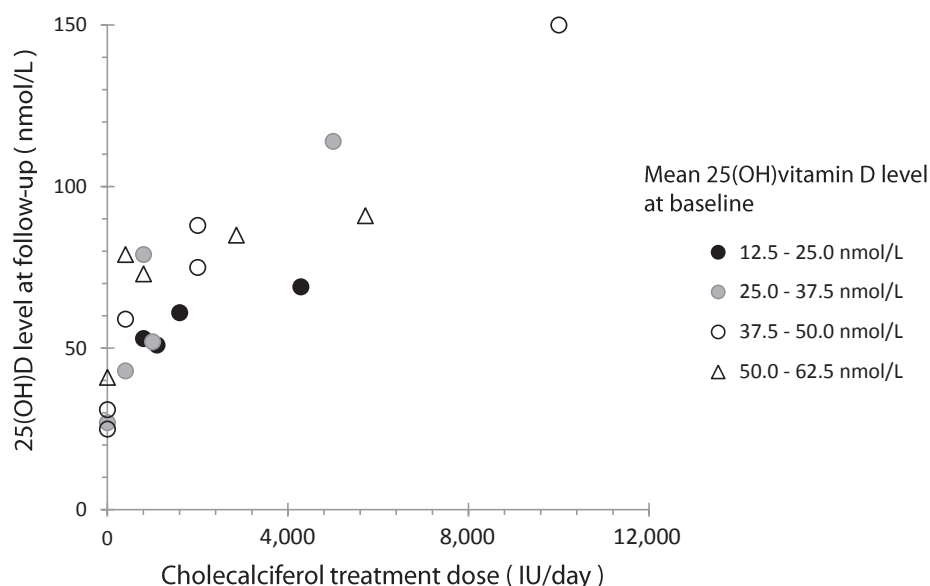
36 BMI; Body Mass Index is calculated from a person's Weight (kilogram) and Height (meter) as  $W / (H)^2$ .

of  $22.5 \pm 11.1$  nmol/L increased to 53 nmol/L and 50.5 nmol/L, respectively (Wicherts et al, 2011).

### 11.5.3. Vitamin D and muscle wellness

The role of serum 25(OH)D levels in maintaining or improving physical performance and muscle strength is still being discussed. The available studies often vary in their populations studied, severity of baseline vitamin D deficiency, and baseline physical functioning (Lagari et al, 2013).

A recent systematic review on vitamin D supplementation showed a small positive effect on muscle strength. Results on muscle strength were significantly more important in baseline 25(OH)D levels < 30 nmol/L (Beaudart et al, 2014). In adults  $\geq 60$  year, studies with daily doses of 800–1,000 IU of vitamin D supplementation showed beneficial effects on muscle strength and balance. An effect on gait was not demonstrated. (Muir et al, 2011).



Until now, the effect of vitamin D on muscle weakness in alcoholic patients has not been investigated. We assume that skeletal muscle function may be more commonly affected in conditions associated with severe vitamin D deficiency of serum 25(OH)D < 20 nmol/L. In fact, vitamin deficiency may reflect less than optimal health in selected populations, such as in chronic alcoholism. For instance, in recent observational studies, hypovitaminosis D was found highly prevalent in critically ill patients and was associated with worse disease severity (Nair et al, 2013). In the general population, low serum 25(OH)D was associated with an excess risk of death compared to 25(OH)D values greater than 50–70 nmol/L (Johansson et al, 2012) in men aged 70–81 years.

#### **11.5.4. Strength and limitations**

Our review links possible interdependent deficiencies of vitamin D, phosphate, and magnesium with muscle weakness in chronic alcoholism. However, since symptoms are rather aspecific, this is no more than an association, which is obviously not the same as a causal relationship. The review may be important because of this connection, but the real proof is in the pudding, by doing further research in clinical trials focusing on possible beneficial effects of vitamin D supplementation and on optimal dosages (Study protocol, Chapter 8).

#### **11.5.5. Conclusion to research question (V)**

Severe vitamin D deficiency probably is a confounder in alcoholic muscle weakness.

#### **11.5.6. Consequenses for daily practice**

We recommend assessment of the vitamin D status in alcoholic patients and supplementation of vitamin D deficiency, when present. Beneficial effects of vitamin D supplementation in chronic alcoholic myopathy remain to be confirmed in clinical trials.

### **11.6. SUGGESTIONS FOR FUTURE RESEARCH**

#### **11.6.1. Delirium, mechanisms, and relation with infections in thiamine deficiency**

We recommend future research focusing on strategies for the early identification of delirium in Wernicke-Korsakoff syndrome and assessment of the temporal progression of delirium including quantification of transitional stages and protracted or persistent delirium.

Although our findings suggest that Wernicke delirium may represent the initial phase of Wernicke-Korsakoff syndrome due to mechanisms of microglial activation, extensive confirmation of these mechanisms requires further research. In order to determine

whether mediating factors in microglial activation, other than thiamine deficiency, may account for an ineffective treatment of the more severe cases of Wernicke encephalopathy, further investigation is warranted.

The interrelationship of infections and thiamine depletion may represent a relevant area for further research in critically ill patients (Manzanares & Hardy, 2011; Ramsi et al, 2014). Early and adequate thiamine supplementation could be helpful to self-neglecting alcoholic patients presenting with infections, confusion, drowsiness, or walking disability.

#### **11.6.2. Neuropathological substrate of Wernicke-Korsakoff syndrome**

In future work we hope to further integrate the concept of Wernicke delirium into a comprehensive description of the neuropathological substrate of Wernicke-Korsakoff syndrome, explaining both delirium and cognitive deficits in terms of alterations or structural disconnectivity of relevant neuronal tracts most vulnerable to the effects of thiamine deficiency.

Yet we do not have a clear view of which neuronal tracts are particularly involved in the mental signs and symptoms of Wernicke-Korsakoff syndrome – e.g., in what way cholinergic tracts of the brainstem are involved in the encephalopathic stage of the syndrome (Cf., Nardone et al, 2013; Vorhees et al, 1977). Our hypothesis of fronto-cerebellar disconnectivity in the end-stage Korsakoff syndrome (supplementary Chapter 9) seems somewhat odd in the context of the thesis, but might be a first step in attempting to more clearly understand the overall symptom profile of Wernicke-Korsakoff syndrome.



## SUMMARY

### Early Detection of Mental and Motor Symptoms In the Wernicke-Korsakoff Syndrome

## 1. WERNICKE-KORSAKOFF SYNDROME

Wernicke-Korsakoff syndrome is a neuropsychiatric disorder consisting of mental confusion and irreversible brain damage caused by vitamin B<sub>1</sub> deficiency. Wernicke encephalopathy – the acute phase of Wernicke-Korsakoff syndrome – is falsely considered as uncommon and is largely misdiagnosed, especially in malnourished alcoholic patients at high risk of developing the disease (Chapter 2 of this thesis; Lemyze et al, 2009). Many cases of Wernicke encephalopathy remain unrecognized until the classic signs of ocular motility impairment, ataxia of gait, and confusion, help to make the diagnosis (Lemyze et al, 2009; Thomson et al, 2009). Unfortunately, these classical signs were found in only 16% of patients with Wernicke encephalopathy (Harper et al, 1986).

## 2. RESEARCH BY SLINGEDAELE KORSKOFF CENTER

Clinical signs of Wernicke encephalopathy most often occur within hours to days before a subsequent hospital admission (Chapter 3 & 6). The emergence of Wernicke encephalopathy may be identified by the presence of a delirium in malnourished alcoholic patients who have trouble walking. In these patients, the delirium is usually due to the vitamin B<sub>1</sub> deficiency among other causes, which may be erroneously diagnosed as alcohol withdrawal delirium (Chapter 2–4). Other heralding symptoms of vitamin B<sub>1</sub> deficiency are the serious infections that are likely to occur during the acute Wernicke phase (Chapter 6).

Physicians may have a limited comfort zone as far as their knowledge of treating patients with alcohol abuse issues. During our hospital visits, we generally heard: “The patient was admitted to the hospital for social reasons, should be transferred to a ‘more appropriate’ department, or needs no further treatment.”

To improve early detection of Wernicke-Korsakoff syndrome, we studied the associations between Wernicke-Korsakoff syndrome (vitamin B<sub>1</sub> deficiency) and:

- The occurrence of delirium (Chapter 2–5).
- The temporal progression regarding gait- and balance impairments (Chapter 4).
- The occurrence of severe infections in the acute Wernicke phase (Chapter 6).

Another vitamin (vitamin D deficiency) may potentially affect muscle health in alcoholism. This topic is worked out in two Chapters:

- Vitamin D deficiency and muscle disease in alcoholism (Chapter 7).
- A research protocol on vitamin D deficiency in alcoholic muscle weakness (Chapter 8).

### **3. THE ANSWERS TO THE RESEARCH QUESTIONS**

The answers to the research questions of Chapter 1 are summarized as follows:

- (I) Wernicke encephalopathy and delirium may be considered synonymous conditions in malnourished alcoholic patients.
- (II) In a detailed case study, the Wernicke-Korsakoff syndrome is highlighted as a neuropsychiatric disorder with mental and motor symptoms that appear in a combined fashion.
- (III) Severe infections were common during the Wernicke phase of Korsakoff patients admitted to Slingsdael Korsakoff Center, Rotterdam.
- (IV) Infection parameters (white blood cell counts, absolute neutrophil counts) might be related to the cognitive outcomes.
- (V) Severe vitamin D deficiency probably is a confounder in alcoholic muscle weakness.

## 4. SUMMARY OF THE CHAPTERS OF THE THESIS

### Chapter 1 – General introduction of Wernicke-Korsakoff syndrome

Korsakoff syndrome is a chronic form of amnesia resulting from thiamine deficiency. The syndrome can develop from unrecognized or undertreated Wernicke encephalopathy. Chapter 1 contains general information on the Wernicke-Korsakoff syndrome and the research questions are listed in this Chapter.

### Chapter 2 – Wernicke delirium mistaken for alcohol withdrawal delirium

Wernicke encephalopathy can easily be mistaken for alcohol withdrawal delirium. Apparently, a history of alcohol abuse influences the diagnosis of patients with delirium, such that Wernicke encephalopathy may be overlooked. In order to identify possible Wernicke encephalopathy in malnourished alcoholic patients, it is essential to give proper attention to any signs of delirium and to problems with gait and posture, as well.

### Chapter 3 – Descriptive study of delirium onset and alcohol withdrawal duration

We presented a descriptive, retrospective study of initial symptoms, comorbidity, and alcohol withdrawal in alcoholic patients with subsequent Korsakoff syndrome. We investigated whether delirium in these patients might be consistent with unidentified Wernicke encephalopathy. In 25/73 (34%) of the patients the classic triad of Wernicke encephalopathy with ocular symptoms, ataxia and confusion, was found. In at least 6/35 (17%; 95%-confidence interval: 10–25%) of the deliria we observed no other underlying causes, thus excluding other somatic causes, medication, (recent) alcohol withdrawal, or intoxication. We suggest that these deliria may have been representing Wernicke encephalopathy without the classic symptoms of ophthalmoplegia, nystagmus, and ataxia. Clinicians must be vigilant for these partial cases, and manage them similarly to patients manifesting the full syndrome. A high frequency (15%) of diabetics may reflect a contributing factor of diabetes mellitus in the evolution of the Wernicke-Korsakoff syndrome.

### Chapter 4 – Detailed case description of mental symptoms and impaired mobility

The intra-individual course of Wernicke-Korsakoff syndrome has not been studied extensively, nor has the temporal progression of gait disturbances and other symptoms of Wernicke encephalopathy. In a detailed case history, we followed the patient's mobility changes and the shifts in his mental status from global confusion and impaired consciousness to more selective cognitive deficits.

Patients with a history of self-neglect and alcohol abuse, at risk of or suffering with Wernicke encephalopathy, should receive immediate and adequate vitamin replacement. Self-neglecting alcoholics who are bedridden may have severe illness and probably active Wernicke encephalopathy. In these patients, mobility changes, delirium, or impaired consciousness can be an expression of Wernicke encephalopathy and should be treated to prevent further damage from the neurologic complications of thiamine deficiency.

### **Chapter 5 – Systematic review of delirium mechanisms**

In this Chapter we further highlighted the linkage between thiamine deficiency and delirium and presented a review of candidate biomarkers of delirium in Wernicke-Korsakoff syndrome and other clinically related conditions – as a possible clue to the pathogenesis of WKS. The earliest biochemical change in Wernicke-Korsakoff syndrome is the decrease of alpha-KGDH activity in astrocytes. According to autopsy-based series, mental status changes are present in 82% of Wernicke encephalopathy cases. The objective of the present review is to identify possible underlying mechanisms relating the occurrence of delirium to Wernicke-Korsakoff syndrome. Studies involving delirium in Wernicke-Korsakoff syndrome, however, are rare. We therefore chose, firstly, to search for candidate biomarkers of delirium irrespective of the clinical setting. Secondly, the results are focused on identification of these biomarkers in reports on Wernicke-Korsakoff syndrome.

In various settings, ten biochemical and/ or genetic biomarkers showed strong associations with the occurrence of delirium. For Wernicke-Korsakoff syndrome, three of these candidate biomarkers were identified, namely brain tissue cell counts of CD68-positive cells as a marker of microglial activation, high cerebrospinal fluid lactate levels, and MHPG, a metabolite of norepinephrine. Based on current literature, markers of microglial activation may present an interesting pathoetiological relationship between thiamine deficiency and delirium in Wernicke-Korsakoff syndrome. The possible loss-of-function mechanisms following thiamine deficiency in Wernicke-Korsakoff syndrome are proposed to come from microglial activation, resulting in a delirium in the initial phase of the syndrome.

### **Chapter 6 – Descriptive study: impact of coincidental infections**

In this Chapter we emphasized the occurrence of coincidental infections and its possible impact on the Wernicke-Korsakoff syndrome. We presented a retrospective, descriptive study of patients admitted to Slingedael Korsakoff Center. We hypothesized that systemic infections in the acute phase are associated with cognitive deficits in patients with Wernicke-Korsakoff syndrome. Patients were selected for further analysis if the onset of the Wernicke-Korsakoff syndrome was clearly documented and if data were

available on white blood cell counts in the acute phase and at least one of six predefined neuropsychological tests on follow-up.

Infections were reported in 35/68 (51%) patients during the acute phase of WKS: meningitis (1), pneumonia (14), urinary tract infections (9), acute abdominal infections (4), septicemia (5) and/ or empyema (1), and infection 'of unknown origin' (4).

The neuropsychological test results showed significant lower scores on the Cambridge Cognitive Examination (CAMCOG) non-memory section with increasing white blood cell counts and on the 'Key search test' of the Behavioral Assessment of the Dysexecutive Syndrome (BADS) with increasing absolute neutrophil counts. We concluded that infections may be a presenting manifestation of thiamine deficiency. Wernicke-Korsakoff patients who suffered from an infection during the acute phase are at risk of worse neuropsychological outcomes on follow-up. These results should, however, be interpreted with caution as the effect estimates were based on a relatively small study population with incomplete data regarding relevant parameters of infection and inflammatory processes.

## **Chapter 7 – Other causes of impaired mobility: review of muscle weakness in alcoholism**

Myopathy refers to a muscular disease in which muscle fibers do not function, resulting in muscular weakness and wasting. Vitamin D deficiency is a well-recognized cause of myopathy, and excessive alcohol consumption is often associated with low or subnormal levels of vitamin D. We reviewed articles on alcoholic myopathy and hypovitaminosis D myopathy and compared the pathophysiological findings in order to 'chart' possible pathways of vitamin D action in the development of alcohol-related myopathy. Based on these results of a strong interdependency of suboptimal levels of vitamin D, phosphate, and magnesium in association with chronic alcohol abuse, we hypothesize that these combined deficiencies interfere with membrane and intracellular metabolic processes in alcohol-related chronic myopathy, although the exact mechanisms remain unclear. While it is possible that vitamin D supplementation may be helpful in prevention and treatment of alcohol-related chronic myopathy, further research is needed to determine if this can improve muscle function if alcohol consumption ceases, and what dosages of vitamin D may be optimal.

## **Chapter 8 – Research protocol of a vitamin D supplementation program in alcoholism**

Decreased bioavailability of vitamins may be due to inadequate dietary sources, lower intestinal absorption and/ or liver dysfunction. Muscular weakness and wasting is frequently found in chronic alcoholism and might be related to severe vitamin D hypovitaminosis. In this Chapter we describe a study protocol to evaluate the effect of vitamin

D supplementation in alcoholic myopathy through intensive outreach in 12 months follow-up.

### **Chapter 9 – Supplementary: a hypothesis on neuronal tracts in Korsakoff syndrome**

We proposed further research on the neuronal connections of the frontal brain and the cerebellum in their relation to cognitive disturbances in Wernicke-Korsakoff syndrome.

### **Chapter 10 – Supplementary: information on thiamine therapy**

Brief description of thiamine treatment dosages and recommendations on intravenous administering of thiamine in Wernicke encephalopathy (in addition to the information of Table 4–4 in Chapter 4).

### **Chapter 11 – General discussion**

In this thesis, we have tried to examine systematically the relation of delirium to the Wernicke-Korsakoff syndrome. The relationship between thiamin deficiency and delirium is complex, as is described in successive paragraphs of this Chapter. Based on observations and suggestions regarding the pathophysiological mechanisms of action, Wernicke-Korsakoff syndrome can be seen as delirium-related cognitive damage. Furthermore, thiamin deficiency is strongly associated with the occurrence of general infections. In this respect, the Wernicke-Korsakoff syndrome is a multidisciplinary disease that requires the collaboration across disciplines – psychiatrists, neurologists, internal medicine physicians, emergency physicians, intensive care physicians, and others.

In daily medical practice, the patients' mental confusion and immobility make the physical examination more difficult. However, the observed combination of impaired mobility and mental disturbances presents a striking feature of Wernicke-Korsakoff disease. In fact, this combination of symptoms may facilitate the early detection of Wernicke-Korsakoff syndrome in malnourished alcoholic patients. Alcoholism and insufficient dietary intake are also associated with other deficiencies than vitamin B<sub>1</sub> deficiency. We paid attention to vitamin D deficiency, which probably can affect muscle mass and muscle strength in chronic alcoholism.

## NEDERLANDSE SAMENVATTING

Vroegsignalering van mentale en motore verschijnselen bij het syndroom van Wernicke-Korsakov

### 1. HET SYNDROOM VAN WERNICKE-KORSAKOV

Het syndroom van Wernicke-Korsakov is een vorm van verwardheid, dat is de ziekte van Wernicke, met daarna vaak een blijvende hersenschade in de vorm van het syndroom van Korsakov. Het syndroom van Wernicke-Korsakov wordt veroorzaakt door vitamine B<sub>1</sub>-gebrek.<sup>37</sup> Het begint dus met verwardheid. En het eindigt met hersenschade.

Er wordt gezegd dat de ziekte van Wernicke vrij weinig voorkomt en dat het syndroom van Korsakov vaak sluipend begint. Maar dat is een misvatting. De verschijnselen van het syndroom van Wernicke-Korsakov ontstaan vaak enkele uren tot dagen voor een ziekenhuisopname. Het begin is te herkennen aan infecties en vooral aan de aanwezigheid van een delier<sup>38</sup> bij een alcoholist die niet kan lopen. De infecties zijn ernstig en komen bij de helft van de mensen in de Wernickefase voor. Het delier komt meestal niet door het stoppen of verminderen van alcoholgebruik, maar wordt door het vitaminegebrek zelf veroorzaakt.

Het syndroom van Wernicke-Korsakov kan ontstaan bij alcoholisten die niet of nauwelijks eten. De medische zorg voor verwarde alcoholisten wordt door hulpverleners in het ziekenhuis meestal niet als chique of uitdagend ervaren. Op de afdeling in het ziekenhuis wordt dan vaak gezegd dat hij/zij tussen wal en schip is gevallen, werd opgenomen met een sociale indicatie of inmiddels is uitbehandeld (Hoofdstuk 1 en 2).

### 2. KORSAKOVCENTRUM SLINGEDAEL

Slingedael biedt Korsakovzorg met verblijf, wonen en welzijn (locatie Slingedael) en observatie, diagnostiek en dagopvang (locatie Tussendael) in Rotterdam. Vanuit Slingedael deden we systematisch onderzoek naar het syndroom van Wernicke-Korsakov (vitamine B<sub>1</sub> gebrek) en:

- Het optreden van het delier (Hoofdstuk 2 t/m 5).
- Het verloop van de loop- en balansstoornissen (Hoofdstuk 4).

37 Een andere naam voor vitamine B<sub>1</sub> is thiamine.

38 Het woord 'delirium' (of delier) komt van het Latijnse: de = vanaf, lira = groef, spoor. Dus van het spoor af, ontspoord. Het is een vorm van verwardheid. Bijvoorbeeld een delier bij koorts = ijlen.

-Het optreden van ernstige infecties (Hoofdstuk 6).

De bedoeling van dit onderzoek was om een beter beeld te krijgen van het syndroom van Wernicke-Korsakov. Dit kan helpen bij een betere herkenning van het syndroom.

Een andere vitamine (vitamine D-gebrek) kan ook van invloed zijn op de balans en spierkracht bij alcoholisme. Dit thema wordt apart uitgewerkt in de daarop volgende hoofdstukken:

-Vitamine D-gebrek en spierziekte bij alcoholisme (Hoofdstuk 7).

-Een plan voor verder onderzoek met vitamine D (Hoofdstuk 8).

### 3. ANTWOORDEN OP DE ONDERZOEKSVRAGEN

De antwoorden op de onderzoeksvragen uit hoofdstuk 1, worden als volgt samengevat:

(I) De ziekte van Wernicke en delier kunnen als synonieme begrippen worden beschouwd bij ondervoede alcoholisten.

(II) Het syndroom van Wernicke-Korsakov is een neuropsychiatrische aandoening met mentale en motore symptomen die met elkaar gecombineerd optreden.

(III) Ernstige infecties kwamen regelmatig voor tijdens de Wernickefase van Korsakov-patiënten, die in Korsakovcentrum Slingsdael werden opgenomen.

(IV) Infectiewaarden tijdens de Wernickefase zijn mogelijk gekoppeld aan de neuropsychologische testresultaten bij het syndroom van Korsakov.

(V) Een ernstig vitamine D-gebrek is een factor om rekening mee te houden bij spierzwakte en alcoholisme.

### 4. SAMENVATTING VAN DE HOOFDSTUKKEN

#### Hoofdstuk 1 – Algemene introductie: het syndroom van Wernicke-Korsakov

Het syndroom van Korsakov is een blijvend geheugenverlies door vitamine B<sub>1</sub>-gebrek. Het syndroom kan ontstaan na een Wernickefase die niet is herkend en niet is behandeld. Hoofdstuk 1 beschrijft algemene informatie over het syndroom van Wernicke-Korsakov en de onderzoeksvragen van dit proefschrift staan in dit hoofdstuk op een rij.

#### Hoofdstuk 2 – Het Wernicke-delier wordt aangezien voor alcoholonttrekkingsdelier

De Wernickefase van het syndroom van Wernicke-Korsakov wordt gemakkelijk verward met een andere aandoening bij alcoholisten, namelijk een delier door stoppen of min-

deren van alcoholgebruik. In dit hoofdstuk wordt een begin gemaakt met de introductie van het delier en de loopstoornissen die voorkomen in de beginfase van het syndroom van Wernicke-Korsakov.

### **Hoofdstuk 3 – Beschrijvend onderzoek: begin van het delier en duur van de alcoholonttrekking**

We beschrijven beginsymptomen, gelijktijdig aanwezige ziekten en eventuele alcohol-onttrekking bij alcoholisten die daarna een Korsakovsyndroom hadden en bij ons werden aangemeld. Uit de beschikbare gegevens onderzochten we of een delier bij deze patiënten overeen zou kunnen komen met een niet-ontdekte Wernicke encefalopathie. Bij 25/73 (34%) van de patiënten kwamen de drie klassieke verschijnselen voor van de ziekte van Wernicke: oogsymptomen, ataxie en verwardheid. Bij ten minste 6/35 is 17% (het 95%-betrouwbaarheidsinterval is 10%–25%) van de delieren vonden we geen andere onderliggende oorzaak, rekening houdend met lichamelijke oorzaken, medicatie en een (recente) alcoholonttrekking of alcoholintoxicatie. We houden het erop dat deze delieren de ziekte van Wernicke vertegenwoordigden zonder de klassieke verschijnselen van een oogspierverlamming, nystagmus en ataxie. Het is van belang deze onvolledige presentatie te herkennen en de patiënten te behandelen, zoals bij de volledige presentatie van de ziekte van Wernicke. Een hoog percentage (15%) diabetespatiënten kan een aanwijzing zijn dat suikerziekte invloed heeft bij een zich ontwikkelend syndroom van Korsakov.

### **Hoofdstuk 4 – Casusbeschrijving: mentale verschijnselen en problemen met het lopen**

Hoe het syndroom van Wernicke-Korsakov bij iemand in de tijd precies verloopt, is niet eerder onderzocht. Het tijdsverloop van de loopstoornissen bij de ziekte van Wernicke is ook niet onderzocht. We beschrijven hier in detail het verloop van de ziekte van Wernicke bij een patiënt die in het begin nog instabiele ziekteverschijnselen had. We volgen de veranderingen van zijn mobiliteit en van zijn mentale situatie die zich wijzigt van een globale verwardheid en een gestoord bewustzijn naar een meer afgebakende schade van de cognitieve functies.<sup>39</sup> Zijn ziekte van Wernicke werd aangeduid als ‘mogelijk’ syndroom van Korsakov en was onvoldoende behandeld volgens de multidisciplinaire richtlijn ‘Stoornissen in het gebruik van alcohol’ van het Trimbosinstituut.<sup>40</sup>

Patiënten met een voorgeschiedenis van zelfverwaarlozing en alcoholmisbruik lopen het risico aan de ziekte van Wernicke te lijden en moeten zo snel mogelijk worden behandeld met de juiste toediening van vitamine B<sub>1</sub>. Zichzelf verwaarlozende, bedlegerige

39 Cognitieve functies van de hersenen zijn bijvoorbeeld iets leren, onthouden, inzien en begrijpen.

40 De richtlijn is te vinden op [www.diliguide.nl/document/1820](http://www.diliguide.nl/document/1820).

alcoholisten hebben waarschijnlijk op dat moment een actieve ziekte van Wernicke, wat een ernstig ziektebeeld is. Een slechte mobiliteit, een delier of een gestoord bewustzijn kunnen bij hen de uiting zijn van de ziekte van Wernicke en moeten als zodanig behandeld worden om verdere schade door de neurologische complicaties van het vitamine B<sub>1</sub>-gebrek te voorkomen.

## **Hoofdstuk 5 – Systematisch literatuuronderzoek van mechanismen bij een delier**

In dit hoofdstuk besteedden we verder aandacht aan de 'link' tussen vitamine B<sub>1</sub>-gebrek en een delier. De vroegste biochemische verandering bij het syndroom van Wernicke-Korsakov is een verlaagde  $\alpha$ -KGDH-activiteit in bepaalde hersencellen, de astrocyten. Volgens hersenenonderzoek bij mensen die aan de ziekte van Wernicke zijn overleden, hadden 82% van hen verschijnselen wat de psychische gesteldheid betreft. Het doel van ons onderzoek is om een overzicht te geven van mogelijke onderliggende mechanismen die een schakel vormen tussen het syndroom van Wernicke-Korsakov en de aanwezigheid van een delier. Er is weinig onderzoek gedaan naar een delier bij het syndroom van Wernicke-Korsakov. Daarom kozen we er bij ons literatuuronderzoek voor eerst naar mogelijke biomarkers<sup>41</sup> van een delier te zoeken, ongeacht de klinische omstandigheden. Vervolgens gebruikten we de aldus gevonden kandidaat-biomarkers voor een zoektocht binnen de literatuur over het syndroom van Wernicke-Korsakov.

Gebaseerd op verschillende patiëntengroepen kwamen er tien biochemische en/of genetische biomarkers naar voren, die een sterk verband vertoonden met het optreden van een delier. Wat het syndroom van Wernicke-Korsakov betreft, kwamen we uit op drie kandidaat-biomarkers voor een delier, namelijk (uit hersenenonderzoek) het aantal CD68-positieve cellen als een marker van microglia-activiteit, verder een hoog lactaatgehalte (in hersenliquor) en ten slotte MHPG, dat is een stofwisselingsproduct van noradrenaline. Microglia zijn cellen die in de hersenen deel uitmaken van het (afweer) systeem voor het opruimen van schade of lichaamsvreemd materiaal. Een ontspoorde microglia-activatie zou een belangrijke schakel kunnen zijn tussen vitamine B<sub>1</sub>-tekort en een delier bij het syndroom van Wernicke-Korsakov. Op grond van de verzamelde literatuur veronderstellen we dat ontregeling van de microglia-activatie een mechanisme is waardoor vitamine B<sub>1</sub>-tekort kan leiden tot een delier en verminderde hersenfunctie bij het syndroom van Wernicke-Korsakov.

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41 Biomarkers zijn meetbare biologische verschijnselen, bijvoorbeeld bepaalde uitslagen van een bloedonderzoek, die gebruikt kunnen worden om de aanwezigheid van een bepaalde ziekte vast te stellen, of het verloop van die ziekte (of de effecten van een behandeling) te volgen.

## Hoofdstuk 6 – Beschrijvende studie: aanwezigheid en gevolgen van infecties

Bij mensen met het syndroom van Korsakov deden we een beschrijvend onderzoek naar de aanwezigheid van infecties tijdens de voorafgaande ziekte van Wernicke. We hadden het idee dat infecties in het lichaam tijdens de beginfase gekoppeld zouden kunnen zijn aan de mate van hersenschade bij patiënten met het syndroom van Wernicke-Korsakov. Doel was om na te gaan of 'markers' van een infectie in de acute Wernickefase, zoals het aantal witte bloedcellen en (voor zover genoteerd) het aantal neutrofiële granulocyten, in verband staan met stoornissen in de cognitieve functies bij het syndroom van Korsakov.<sup>42</sup>

Er werd gekeken naar ontslagbrieven van voorafgaande opnames in een ziekenhuis en gezocht naar gegevens over infecties tijdens de acute Wernickefase. De gegevens werden gebruikt als uit de ontslagbrief kon worden opgemaakt wanneer het syndroom van Wernicke-Korsakov was begonnen. En als tijdens die eerste fase bloedonderzoek was gedaan met in ieder geval een bepaling van het aantal witte bloedcellen. Verder hadden we van tevoren een keus gemaakt welke neuropsychologische testresultaten we wilden hebben. Het gaat om een beperkte set van zes testen (screeningsinstrumenten en neuropsychologische testen), waarvan we verwachtten dat één of meer van die testen gedaan waren. Infecties waren beschreven bij 35/68 is 51% van de patiënten tijdens de beginfase van het syndroom van Wernicke-Korsakov. Bij deze 35 patiënten kwamen de volgende infecties voor: hersenvliesontsteking (kwam één keer voor), longontsteking (14 keer), urineweginfecties (9), acute buikinfecties, waaronder buikvliesontsteking (4), bloedvergiftiging (5) en/of pus in een bestaande lichaamsholte (1) en infecties waarvoor geen oorzaak is gevonden (4).

Niet bij alle patiënten waren alle zes neuropsychologische testen gedaan. De wel aanwezige neuropsychologische testresultaten lieten significant lagere scores zien op dat onderdeel van de 'Cambridge Cognitive Examination' (CAMCOG) dat niet het geheugen testte: bij toename van de witte bloedcellen werd met de Spearman rangcorrelatie coëfficiënt (Rho) een matig sterk maar significant verband gevonden met lagere uitkomsten van deze CAMCOG-score (Rho is -0,34 met een 95%-betrouwbaarheidsinterval van -0,57 tot -0,06 in een groep van 44 patiënten). Verder werd op een ander testonderdeel, namelijk de Sleutelzoektest van de 'Behavioral Assessment of the Dysexecutive Syndrome' (BADS) een sterk en significant verband gevonden met lagere scores op de Sleutelzoektest bij toename van het aantal neutrofiële granulocyten (Rho is -0,85 met een 95%-betrouwbaarheidsinterval van -0,97 tot -0,42 bij negen patiënten bij wie deze bloedbepaling bekend was).

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42 De neutrofiële granulocyt is een type witte bloedcel dat vooral in aantal toeneemt bij een infectie door bacteriën. Cognitieve functies van de hersenen zijn, zoals eerder vermeld, bijvoorbeeld iets leren, onthouden, inzien en begrijpen.

Infecties kunnen de uiting zijn van vitamine B<sub>1</sub>-gebrek. Patiënten bij wie zich het syndroom van Wernicke-Korsakov ontwikkelt, lopen kans op slechtere neuropsychologische uitkomsten als er in de beginfase infecties aanwezig waren.

### **Hoofdstuk 7 – Spierzwakte bij chronisch alcoholisme: een literatuuronderzoek**

Het woord 'myopathie' wordt gebruikt voor spierziekte waarbij spiervezels niet goed functioneren, wat zich uit in spierzwakte en verlies van spierweefsel. Een tekort aan vitamine D is een bekende oorzaak van myopathie. Omdat overmatig alcoholgebruik vaak gepaard gaat met te lage waarden van vitamine D, zochten we naar een verband tussen vitamine D-gebrek en de myopathie door alcoholgebruik. We keken naar artikelen over 'alcoholische myopathie' en/of 'myopathie door vitamine D-gebrek' in the PubMed-bibliotheek van januari 1985 tot en met september 2011. We bestudeerden de teksten op het gebied van de pathofysiologie met de bedoeling om een aanwijzing te vinden voor mogelijke werkingsmechanismen van vitamine D binnen de alcoholische myopathie.<sup>43</sup>

In geval van langdurig alcoholmisbruik vonden we een samenhang tussen verlaagde waarden van de volgende drie stoffen: magnesium, fosfaat en vitamine D. We vermoeden dat de combinatie van deze tekorten van invloed zou kunnen zijn bij chronische alcoholische myopathie. Het precieze werkingsmechanisme is niet duidelijk. Hierbij kan gedacht worden aan negatieve effecten van deze tekorten op de stofwisselingsprocessen van de spiercellen. Mogelijk kan een behandeling met vitamine D een bijdrage leveren bij de preventie en behandeling van chronische alcoholische myopathie.

### **Hoofdstuk 8 – Onderzoeksprotocol: vitamine D-verstreking bij alcoholisme en vitamine D-tekort**

Ons lichaam kan vitamines tekort komen door onvolwaardige voeding, een verminderde opname door de darm en/of een gestoorde leverfunctie. Spierzwakte en verlies van spiermassa komen veel voor bij chronisch alcoholisme en zouden gekoppeld kunnen zijn aan een ernstig vitamine D-gebrek.

Dit hoofdstuk beschrijft een onderzoeksprotocol van een vitamine D-programma gericht op het behandelen van vitamine D-tekorten. Kandidaat-deelnemers aan het programma zijn mensen uit de algemene bevolking met bekend alcoholisme en een risico op (meerdere) vitaminetekorten. Deelnemers met een vitamine D-deficiëntie van < 50 nmol/L serum-25-hydroxyvitamine D (25(OH)D) worden per loting toegewezen aan één van de volgende twee behandelstrategieën: (i) Het 'Vitamin D Intensive Outreach' (VIDIO)-programma bestaande uit een colecalciferol-oplaaddosering en een hoge dosering colecalciferol die tweemaandelijks wordt uitgereikt door de Straatdokter.

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43 Pathofysiologie, dat is (kennis van) een door ziekte verstoorde lichaamsfunctie.

ter van de GGD in Rotterdam. En de andere lotinguitkomst is: (ii) 'Care As Usual' (CAU) bestaande uit een recept voor dagelijks colecalciferol 800 I.E. (in combinatie met 500 mg calciumcarbonaat) – waarvan de effectiviteit mede afhangt van de medicatietrouw van de deelnemer. De VIDIO-interventie is gebaseerd op algemene principes om de medicatietrouw ten behoeve van een succesvolle behandeling te vergroten, gevolgen van ziekte te voorkomen, en gezondheid te verbeteren, met een laagfrequente medicatietoediening in één-op-één patiëntcontacten.

Primaire uitkomstmaten van het onderzoek zijn de 25(OH)D concentraties. Secundaire uitkomstmaten zijn krachtmetingen van de quadricepsspier, een oriënterend onderzoek van het lopen en staan van de deelnemer, de resultaten van een cognitieve screening en een beoordeling van ziekte-gerelateerde kwaliteit van leven. Voor de factoren die van invloed zouden kunnen zijn op de vitamine D-inname wordt gekeken naar algemene kenmerken van de deelnemer, alcoholgebruik, leverfunctie en andere laboratoriumresultaten en onder andere zelfredzaamheid en sociale steun. Een vergelijking tussen de twee strategieën van vitamine D-toediening en serum-25(OH)D-waarden geeft inzicht in de effectiviteit van de interventie. Verbetering van spierkracht in de VIDIO-interventie geeft een indruk over een effect van vitamine D.

## **Hoofdstuk 9 – Supplement: hypothese over zenuwbanen en het syndroom van Korsakov**

Op basis van het cognitieve profiel van stoornissen die volgens de literatuur voor kunnen komen bij beschadiging van de kleine hersenen, deden we suggesties om de cognitieve stoornissen van het syndroom van Wernicke-Korsakov te zoeken in zenuwbanen die de voorste hersengebieden en de 'uitvoerende hersenfuncties' verbinden met de kleine hersenen.

## **Hoofdstuk 10 – Supplement: enige informatie over de behandeling met thiamine**

Beknpte informatie over de vitamine B<sub>1</sub> (thiamine) doseringen bij de behandeling van de ziekte van Wernicke en adviezen voor de intraveneuze toediening ter aanvulling op de informatie in hoofdstuk 4 (Tabel 4–4).

## **Hoofdstuk 11 – Algemene discussie van de inhoud van dit proefschrift**

Sommige auteurs hebben zich afgevraagd of onder de symptomen van het Wernicke-Korsakov syndroom een delier zou schuilgaan (Djelantik et al, 2015) en anderen veronderstelden dat de diagnose delirium tremens in sommige studies op een vergissing zou kunnen berusten (Cook et al, 1998). In dit proefschrift hebben we getracht systematisch na te gaan wat een delier is in relatie tot het syndroom van Wernicke-Korsakov. De relatie tussen thiaminegebrek en een delier is complex, wat in meerdere paragrafen in

dit hoofdstuk uitvoeriger uiteen wordt gezet. Het syndroom van Wernicke-Korsakov is op basis van de observaties en suggesties met betrekking tot het werkingsmechanisme, op te vatten als een voorbeeld van delier-gerelateerde cognitieve schade.<sup>44</sup> Verder is een thiaminegebrek sterk geassocieerd met het optreden van algemene infecties. Hiermee wordt het syndroom van Wernicke-Korsakov een multidisciplinaire aandoening voor de psychiater, de neuroloog, de internist, de eerstehulparts, de intensivecarearts en anderen.

In de dagelijkse medische praktijk is de zichzelf verwaarlozende alcoholist, die verward en bedlegerig is geworden, moeilijk te onderzoeken. De koppeling tussen verstoorde mobiliteit en mentale stoornissen is echter een opvallend ziektekenmerk. De combinatie van het delier en de verstoorde mobiliteit bij een zichzelf verwaarlozende alcoholist zou de vroege herkenning van het syndroom van Wernicke-Korsakov kunnen vereenvoudigen.

Onvolwaardige voeding bij alcoholisme kan tot meer deficiënties leiden dan vitamine B<sub>1</sub>-gebrek. In dit verband wordt ook aandacht besteed aan vitamine D-tekort, dat van invloed zou kunnen zijn op het verlies van spierkracht en dunner worden van spieren bij chronisch alcoholisme.

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44 Vergelijking met: Schmitt EM, Marcantonio ER, Alsop DC, et al. 2012. Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *J Am Med Dir Assoc*. 13:818.e1–10.

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## CURRICULUM VITAE

Jan W. Wijnia is specialist ouderengeneeskunde in Korsakovcentrum Slingedael in Rotterdam. Geboren in 1959 te Enkhuizen. Gehuwd met Cari van Triest. Drie kinderen Geeke, Arjen en Ieke.

Als opleiding Gymnasium-B in Apeldoorn. Studie geneeskunde en Verpleeghuisarts-opleiding (specialist ouderengeneeskunde) aan de Vrije Universiteit in Amsterdam.

Verdere werkzaamheden waren in Geriatrisch centrum Antonius Binnenweg, Rotterdam, ondermeer revalidatie, palliatieve zorg en verpleeghuiszorg. Arts sociale psychiatrie bij RIAGG Zuidhage en acute dienst in Den Haag. Arts-assistent neurologie in het Academisch Medisch Centrum en Onze Lieve Vrouwe Gasthuis in Amsterdam. Als arts begonnen bij de St. Kruispost, medische hulpverlening voor onverzekerden, Oudezijds Voorburgwal in Amsterdam. Verder is Jan Wijnia opleider specialist ouderengeneeskunde.

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## PORTFOLIO

Scholing		
20-3-2012	-Boerhaave nascholing, Leiden: 'Gewogen en te licht bevonden' over onderzoeksprotocollen die niet werden goedgekeurd door de Commissie Medische Ethiek van het LUMC 1998–2010	8 uur
12-12-2014	-Symposium 'Alcohol en Cognitie', Vincent van Gogh GGZ, Venray/ Venlo	8 uur
2009	Idem	8 uur
2000	-Module wetenschappelijk onderzoek tijdens de opleiding tot verpleeghuisarts	24 uur
Bestudeerd	-Dassen e.a. Lezen en beoordelen van onderzoekspublicaties. Tieme, Meulenhoff, 1992	40 uur
	-Zielhuis e.a. Handleiding medisch-wetenschappelijk onderzoek. Bunge, 1995	
	-Walvoort e.a. Het schrijven van een medisch-wetenschappelijk artikel. Bohn, Stafleu, van Loghum, 2010	
Disseminatie van kennis, gegeven scholing		
30-5-2012,	-Presentaties (3x) voor Medilex nascholing 'Troebel brein'	24 uur
27-11-2012 & 2013	-en 3x verdiepingssessies, Utrecht	24 uur
2012–2014	-Presentaties (3x) voor wetenschappelijk onderzoek bijeenkomsten van het Korsakov kenniscentrum	24 uur
5-2-2012	-Regiobijeenkomst vereniging specialisten ouderengeneeskunde (Verenso) Zuid-Holland-Zuid, presentatie	4 uur
12-3-2013	-Scholingsprogramma voor AIOS ouderengeneeskunde	6 uur
11-4-2014	-Presentatie op refereerbijeenkomst Tactus verslavingszorg voor verslavingsartsen KNMG, Deventer	6 uur
26-3-2015	-Netwerkbijeenkomst Korsakov België-Nederland, Breda	6 uur
2010–2015	-Scholing in het kader van de accreditatie/herregistratie als specialist ouderengeneeskunde	200 uur
2014–2015	-Kaderopleiding voor opleiders specialist ouderengeneeskunde, SOON, Utrecht	74 uur



## PUBLICATIES

1. Wijnia JW, Oudman E, Bresser EL, Gerridzen IJ, van de Wiel A, Beuman C, Mulder CL. Need for early diagnosis of mental and mobility changes in Wernicke encephalopathy. *Cogn Behav Neurol*. 2014; 27:215-221.
2. Oudman E, Van der Stigchel S, Nijboer TC, Wijnia JW, Seekles ML, Postma A. Route learning in Korsakoff's syndrome: Residual acquisition of spatial memory despite profound amnesia. *J Neuropsychol*. 2014 Oct 26. [Epub ahead of print].
3. Oudman E, Postma A, Van der Stigchel S, Appelhof B, Wijnia JW, Nijboer TC. The Montreal Cognitive Assessment (MoCA) is superior to the Mini Mental State Examination (MMSE) in detection of Korsakoff's syndrome. *Clin Neuropsychol*. 2014; 28:1123-1132.
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## VERKLARENDE WOORDENLIJST

**Achterhersenen.** Weinig gebruikte omschrijving van het ‘metencephalon’, een deel van de hersenen bestaande uit de pons (Zie **Pons**) en de kleine hersenen (Figuur 9–2).

**Ataxie** (Grieks). Ongecoördineerd verlopende beweging van armen, romp of benen. Stoornissen in de coördinatie komen voor bij stoornissen van de kleine hersenen. Een voorbeeld is een dronkemansgang die bij de ziekte van Wernicke ook zonder alcohol kan voorkomen. Zie ook: Dysartrie en Nystagmus.

**Biomarkers.** Biomarkers zijn meetbare biologische verschijnselen, bijvoorbeeld bepaalde uitslagen van een bloedonderzoek, die gebruikt kunnen worden om de aanwezigheid van een bepaalde ziekte vast te stellen, of het verloop van die ziekte (of de effecten van een behandeling) te volgen.

**Cerebellum** (Latijn). De kleine hersenen (Zie figuur 9–2).

**Cerebellar** (Engels), cerebellair. Met betrekking tot de kleine hersenen.

**Cholecalciferol** (Engels), colecalciferol (Nederlands). Een vorm van vitamine D afkomstig uit de voeding en het lichaam maakt dit zelf aan in de huid onder invloed van (ultraviolet) licht.

Colecalciferol wordt door de lever omgezet naar 25-hydroxyvitamine D = 25(OH) D, dat door de nier wordt omgezet naar de actieve vorm 1 $\alpha$ , 25-dihydroxyvitamine D = 1,25(OH)<sub>2</sub>D.

**Cognition** (Engels), cognitie. Kennende functies van de hersenen, zoals leren, onthouden, onderkennen, enz.

**Coma** (Grieks). Toestand van verlaagd bewustzijn. Bewusteloosheid.

**Decussating tracts** (Engels). **Decussatio** (Latijn = een kruiselings verloop, kruising). Kruising van zenuwbanen uit (gelijknamige) linker en rechter hersengebieden. Bijvoorbeeld: de ‘midden’ in de hersenstam gelegen overkruising van de zenuwvezels komend uit de linker en rechter rode kern.

**Delirium**, delier (Latijn: **de** = vanaf, **lira** = groef, spoor). Van het spoor af, ontspoord. Een vorm van verwardheid. Bijvoorbeeld: een delier bij koorts = ijlen.

**Delirium tremens** is alcoholonthoudingsdelier, alcoholonttrekkingsdelier. Delier na het staken of na een vermindering van voorheen fors en/of langdurig alcoholgebruik; is afgezien van de oorzaak klinisch niet goed te onderscheiden van een delier door andere oorzaken (Tabel 3–1 en Van den Brink & Jansen, 2009, blz. 248).

**Dementie** (Latijn: **de** = naar beneden, **mens** = geest). Afbrokkeling, aftakeling van de geestelijke vermogens.

**Diaschisis** (Grieks). Verstoorde functie van een hersengebied door beschadigde verbindingen met andere hersengebieden.

**Dysartrie** (Grieks). Ongecoördineerd verlopende spraak die moeilijk is te verstaan door verstoorde articulatie.

**Empyeem** (Grieks). Pusophoping (etter) in een bestaande lichaamsholte, bijvoorbeeld de borstkas, galblaas, urineblaas.

**Encephalopathy** (Engels), encephalopathie, encefalopathie (Grieks: **en** = in, **cep(h)** = 'kop', **-pathie** = aandoening of aandoenlijk). Dus een omschrijving voor: hersenaandoening.

**Korsakoff** (Engels), Korsakov, Korsakow. Russische neuroloog in de 19<sup>e</sup> eeuw.

**Korsakoff's** (Engels). Bedoeld is syndroom van Korsakov (Zie tabel 3–1).

**Mentale, mentaal** (Latijn: **mens** = geest), verschillende betekenissen. Hier: met betrekking tot de geestesgesteldheid.

**Mental symptoms** (Engels). Psychische klachten of verschijnselen.

**Microglia** (Grieks). Microglia zijn cellen die in de hersenen deel uitmaken van het (afweer)systeem voor het opruimen van schade of lichaamsvreemd materiaal.

**Motor** (Engels), motor, motorisch (Nederlands). Op beweging betrekking hebbend.

**Myopathy** (Engels), myopathie (Grieks: **myos** = spier). Dus een omschrijving voor: spierziekte.

**Nucleus ruber** (Latijn), rode kern. Een groep zenuwcellen (links en rechts) in de hersenstam, met een kleur die zou komen door ijzerpigmenten.

**Nystagmus** (Grieks). Ongecoördineerd (schokkend) verlopende oogbewegingen.

**Ophthalmoplegie** (Grieks), op verschillende manieren gespeld: ph = f, th = t. Ophthalmoplegie is zwakte of verlamming van de oogbewegingen. Ophthalmoplegie kan zich uiten in dubbelzien.

**Pathogenese** (Grieks). De wijze waarop een ziekte ontstaat.

**Pons** (Latijn) = brug. Deel van de hersenstam dat een verbinding vormt met de kleine hersenen.

**Quadriceps** (Latijn), voluit: 'musculus quadriceps femoris'. Bovenbeenspier; deze strekt de knie. Voorbeelden van de functie van de quadricepsspier zijn: opstaan, lopen, traplopen.

**Sepsis** (Grieks). 'Bloedvergiftiging'. Een levensbedreigend ziektebeeld door aanwezigheid en vermeerdering van bacteriën in het bloed.

**Somnolentie** (Latijn). Sufheid, slaperigheid.

**Syndrome** (Engels), syndroom. Samenstel van ziekteverschijnselen die als eenheid (ziekte) worden opgevat. Bijvoorbeeld: syndroom van Korsakov.

**Thiamine** is vitamine B<sub>1</sub>.

**Wernicke**. Duitse neuroloog in de 19<sup>e</sup> eeuw. Zijn naam is ondermeer verbonden aan het ziektebeeld Wernicke encefalopathie (Zie Tabel 3–1), een levensbedreigende hersenaandoening door vitamine B<sub>1</sub> gebrek.

**Wernicke-Korsakoff syndrome** (Engels), is de combinatie van de twee ziektebeelden: 1. De ziekte van Wernicke (is Wernicke encefalopathie) en 2. Het syndroom van Korsakov.

**Ziekte van Wernicke** is Wernicke encefalopathie.

