Korsakoff Syndrome: A Chronic Nutritional Deficiency Neuropsychiatric condition

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ABSTRACT

In this review we have focused on Korsakoff syndrome, which is an aftermath of Wernicke encephalopathy (WE). Wernicke-Encephalopathy is neuropathologically marked by thiamine or vitamin B_1 deficiency, typically induced by excessive alcohol use over an extended period of time in alcoholic patients, while in Nonalcoholic patients, it may be due to impaired utilization or accelerated usage of thiamine. Wernicke-Korsakoff syndrome (WKS) affects the brain region such as the mammillary bodies, periaqueductal and periventricular grey matter, colliculi bodies, and thalamus. The classic triads of WE are ophthalmoplegia, Nystagmus, and ataxia. The brain is examined using MRI and shows damage to the nuclei or memory transit- papez circuit that connects mamillary bodies to the anterior thalamus using the mammillothalamic tract responsible for the recollective memory in the diencephalon. Patients can be treated by parenteral thiamine administration and by abstinence of alcohol within their lifestyle.

Keywords: *Korsakoff Syndrome, alcoholic, non-alcoholic, Alzheimer's, memory-loss Wernicke encephalopathy, Wernicke-Korsakoff syndrome.*

INTRODUCTION

Korsakoff syndrome (KS) develops in patients with unrecognized and untreated Wernicke encephalopathy [1]. Wernicke encephalopathy can be caused by AIDS, cancers like gastric and colon cancer, recurrent infections, malnutrition, starvation, eating disorders, and other conditions like gastric bypass surgery, Hyperemesis gravidarum, etc. The Korsakoff syndrome is typically preceded by an episode of Wernicke encephalopathy, where progressive brain lesions occur to severe thiamine deficiency. The KS does not usually appear following a specific Wernicke event but also because of a recent head injury or chest illness, and some individuals begin comatose or semi-conscious. Doctors may fail to recognize Korsakoff syndrome until the acute disease has resolved, resulting in delayed or inefficient treatment [2].

KS is a majorly irrecoverable residual chronic condition resulting from severe vitamin B1 deficiency and arising after insufficient recovery from Wernicke encephalopathy, best described by an abnormal mental state in which explicit memory is influenced out of all proportion to other cognitive abilities from an otherwise alert and responsive patient, whose mental build may be further distinguished by executive dysfunctions. [3]

History:

Sergei Korsakoff, a Russian neuropsychiatrist, was the man who coined the term "Korsakoff syndrome". Vitamin B1 deficiency syndrome is said to have been first mentioned in Robert Lawson's report published in 1878. [4]. Korsakoff was the first to introduce a detailed description of the syndrome in a systematic review of the literature authored around 1887 and 1891[5], [6], [7] and [8]. There are approximately two-thirds of all cases attributed to Alzheimer's disease (AD), with the remaining one-third attributed to vascular dementia and mixed dementia [9], [10], and [11]. A memory disorder, according to Korsakoff, occurs when patients are in a normal state of consciousness and appears to have complete control over all of their faculties when conversing with others, but suffers from severe impairments in current and recent memory, such as repeating questions, having to read the very same page for hours at a stretch, and unable to remember people they have met repeatedly since the appearance of the disease. Pathologic causes of multiple neuritis can impact both central and peripheral nerve systems, causing symptoms of either neuritis or brain changes. [12]. Even Korsakoff realized that in some cases, "the complete sickness reveals itself exclusively by psychic symptoms" by 1889.

An observation of undernourished captives during a war by de Wardener and Lennox (1947), vitamin b1 deficiency is causing the acute Wernicke episode, accompanied by Korsakoff's syndrome. [3].

Epidemiology

Alcoholic patient:

In 2016, there were roughly 1 million instances of alcoholism in the United States, and 99 million disability-adjusted life years (DALY) were lost as a result [13]. Alcoholism is the third most common preventable cause of death in the United States. Because alcohol-related death is more common in young and middle-aged people (15–49 years), where it is the

leading cause of DALYs [14], it is even more worrying. Alcohol was drunk by 2.3 billion individuals worldwide in 2016, according to the World Health Organization. The amount of alcohol consumed per capita increased from 5.5 liters in 2000 to 6.4 liters in 2016 in the United States. However, the proportion of drinkers is increasing in India and China, Western Pacific, Europe, and South-East Asian countries [15]. Alcohol consumption demographics are also altering, with younger drinkers and more women consuming. Around 200 diseases and injuries have been related to alcohol, including Korsakoff syndrome, cardiovascular ailments, cirrhosis, and numerous cancers [15].

Thiamine insufficiency may be linked to alcohol-induced brain damage in alcoholics [16], [1], and [17] treatment of Wernicke encephalopathy in alcoholics necessitates greater thiamine doses and indicates a more severe thiamine deficiency [18]. It has also been argued that because their symptoms are more evident, nonalcoholics may be more quickly recognized with thiamine insufficiency [1], [17]. As a result, the therapy response is more rapid and powerful. In non-alcoholics, a single incident of thiamine deficiency can produce WKS, whereas many bouts can cause WKS in alcoholics [19].

Nonalcoholic patients

Nonalcoholic patient incidence estimates are even more constrained due to the longitudinal nature of such research and the intrinsic difficulty of detecting non-epidemiology when applied repetitively, reproducibly, and conveniently in large populations. Existing research is diverse in terms of methodology and data [20].

Obesity raises the likelihood of Korsakoff syndrome in nonalcoholic patients, emphasizing the pathophysiological relationship between the two. Nonalcoholic individuals' obesity ranges from overweight to obese and very fat. BMI, the most generally used obesity proxy, has typically shown an increasing trend over the preceding decades, with the greatest growth in low- and middle-income countries, primarily in Asia and Africa [21], [22]. Among nonalcoholic patients, a similar pattern emerges, with Countries in Asia containing the majority of an additional patient load. Globalization's long-term cultural effects on eating patterns include overconsumption of refined carbohydrates, food products, and calorie-dense preservatives.

Signs and Symptoms:

Korsakoff's syndrome (KS) is categorized by dense anterograde amnesia induced by diencephalon damage, which is generally caused by chronic alcohol abuse and thiamine deficiency. Several measures of procedural memory are impaired in KS patients, most likely due to neurological dysfunction in cognitive processes associated with alcohol-related neurological damage outside of the diencephalon. [23]

Korsakoff syndrome is caused by persistent impairment of memory-related regions of the brain. The symptoms of Korsakoff syndrome include:

- Inability to create new memories
- Confabulations- create fictitious experiences to help make up for memory impairment
- Hallucinations
- Cognitive and behavioral symptoms

- Changes in mental status (up to 82 percent of patients) - disorientation, amnesia, and delusory behaviors, procedural memory dysfunctions, semantic memory dysfunctions, executive dysfunctions, etc.
- Dysfunctions of the oculomotor system – Nystagmus (most frequently horizontal Nystagmus), retinal hemorrhage, ophthalmoplegia, IV cranial nerve palsy, and conjugate gaze.
- Ataxia - a broad-based gait [24]

Korsakoff syndrome is distinguished from Wernicke encephalopathy by anterograde amnesia, which severely limits one's potential for learning, retrograde amnesia, and executive deficiencies, which result in decreased inhibition and difficulty with judgement, planning, and problem-solving [25]. Anterograde amnesia is commonly manifested by confabulations, in which incorrect information is utilized to fill in holes in one's memory [26].

Table 1: The Clinical Diagnosis of WE Using Operational / Caine Criteria [23].

Symptoms or Signs	**As evidenced by one or more of the following**
Dietary Deficiency	Undernutrition (BMI<2SD below normal) History of grossly impaired dietary intake An abnormal thiamine status
Oculomotor abnormalities	Ophthalmoplegia Nystagmus Gaze palsy
Cerebellar Dysfunction	Ataxia Abnormalities of past pointing Dysdiadokokinesia Impaired heel-shin testing
Alternation in mental status	Disorientation in two of three fields Confused An abnormal digit spans Comatose

Etiology and Neuropathology

Korsakoff syndrome being an after math of Wernicke encephalopathy, it is very important to understand the pathology of WE. WE develop when vitamin b1 levels are low in gastrointestinal conditions, cancer, regurgitation seen in during (Hyperemesis gravidarum), after chemotherapies treatments, systemic ailments such as Human immunodeficiency virus and other opportunistic infections, renal illnesses, hypothyroidism, and hypo magnesia – regardless of alcohol consumption. In those conditions, the prevalence of WKS may be as intense as the prevalence of alcohol use problems. [23].

Thiamine, or vitamin B1, is a source of nutrient required by every body tissue, including that of the central nervous system. Chicken meat, whole grain products, and chick peas, legumes, and soybeans are all high in thiamine. Many foods in the United States, including breads and cereals, are fortified with thiamine. As a result, the vast majority of people consume adequate

amounts of thiamine. The average individual consumes 0.2 g per day; the RDA for men is 0.0012g per day and 0.0011g per day for women. [27]

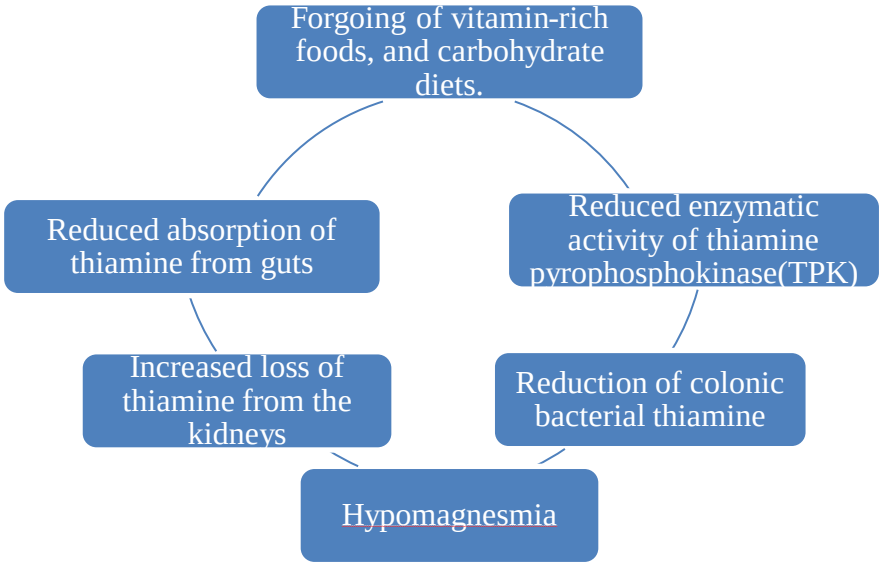

Figure1. Factors for Thiamine deficiency in alcoholic patients: [28]

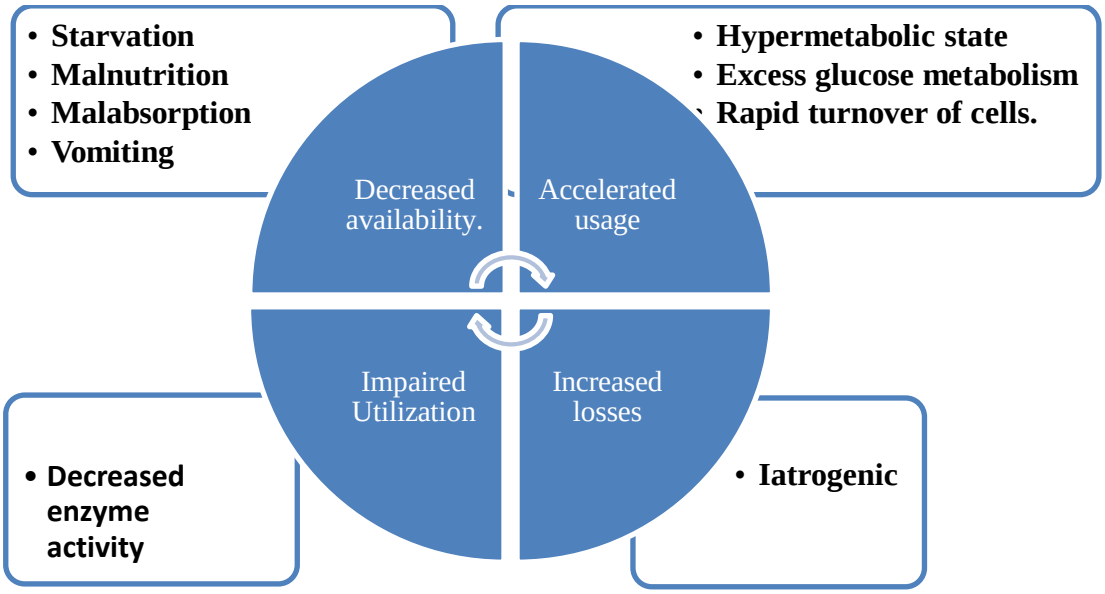

Figure2. Factors for Thiamine deficiency in nonalcoholic patients: [28]

Within four days, a thiamine deficiency in the brain causes cerebral oedema, cerebral ischemia and a boost in astroglia volume. Reduced transketolase activity causes vascular endothelial dysfunction, N_2O production, and the release of intracellular glutamate into the extracellular space after 7 to 10 days. Due to the lack of osmotic gradients and the production of free radicals, vasogenic swelling and BBB permeability develop. Neuronal DNA fragmentation and lactic acidosis cause irreversible structural damage and neuronal necrosis after 14 days of thiamine deficiency. [28]

Memory is a complex network of cortical and subcortical nuclei linked by white matter pathways. While looking at lesions in any of the nuclei or tracts is beneficial, focusing simply on one location does not fully reflect the memory circuit's connections. Alcohol-Induced

Brain Atrophy - One theory holds that the neurotoxic effects of alcohol may cause deformation of the cerebral cortex and white matter and potential atrophy of basal forebrain regions. Hypothalamic damage has been linked to vitamin b1 deficiency (perhaps because blood vessels break in that region). As per this supposition, addicts who are vulnerable to alcohol poisoning may suffer from perpetual or ephemeral cognitive impairments as a result of brain deformation. Someone who is susceptible to vitamin b1 deficiency will have a fairly benign or ephemeral neurocognitive disorder, with short-term dementia seeming to be the most noticeable symptom. Patients with double debility, defined as a combined effect of alcohol neuronal death and vitamin b12 deficiency, will have massive brain vandalism, including deep neural pathways such as within the limbic system. Individuals with this condition will experience severe primary or active cognitive impairment as well as collateral mental disabilities. [29] Brain abnormalities may be produced by alcoholism alone or by a combination of nutritional deficiencies and persistent drinking. Inadequate thiamine or other nutritional deficiencies could be contributing to the wide variety of presenting symptoms and neuroradiological characteristics [30]. Frequently binge drinking alcoholics risk nutritional deficiencies [31]. A recent study found that low-quantity–higher-frequency drinkers had the best diet quality. Drinking habits have little to do with diet [32].

Due to the fact that alcoholism is a chronic condition that frequently lasts decades, it is critical to assess the impact of aging-related brain involution. In aged drinkers, the prefrontal cortex may demonstrate long-term volume reduction and atrophy [33], [34]. While sustained abstinence has been shown to partially cure alcohol-related brain abnormalities [35], the extent to which KS healing occurs is unknown. Hence, figure 3 shows the alcoholism-related abnormalities in the brain.

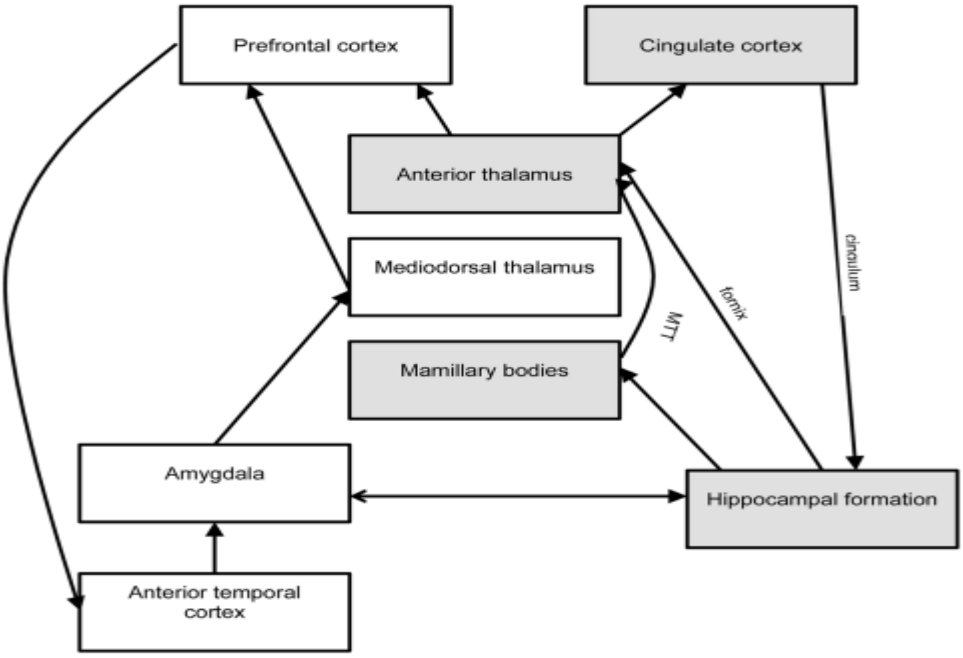

Figure 3: Memory-related brain areas and connections [36]

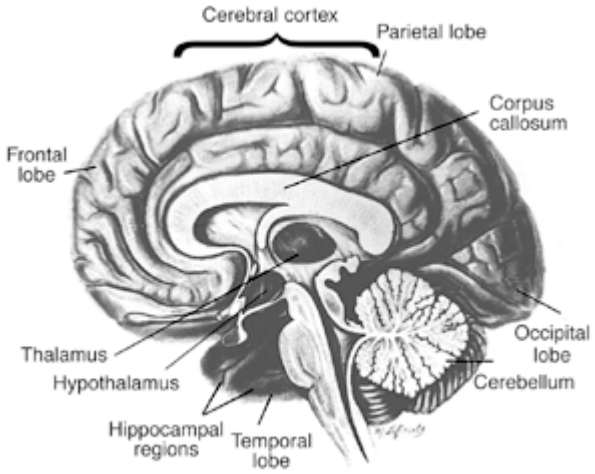

Figure 4: Brain areas susceptible to alcoholism.[37]

Despite the fact that neuropathological examinations of well-characterized KS patients have provided insight into the shape and pattern of aetiology in Korsakoff Syndrome, the area or areas of disease required and sufficient to induce KS remain unknown. Furthermore, neither the mechanism(s) by which the cells are harmed nor the reasoning behind the geographic vulnerability is known. [36].

These changes can conceal fundamental disorders and lead to inaccurate diagnoses. Another issue is the significant decline of autopsies throughout the decades. Patients who are chronically unwell are rarely autopsied, limiting the use of modern histological and molecular methods. New imaging techniques have improved in vivo diagnosis of WKS and enabled the investigation of brain connections and architecture in real-time [36].

A microscopic examination of a KS patient's brain reveals apparent disease. The mammillary bodies shrink and darken, and the ventricular system dilates in most individuals. The third and fourth ventricles are encircled by grey hyperpigmentation that suggests necrosis. The most evident microscopic trait is gliosis, which is caused by increased cell packing density caused by atrophy [38] was observed in some patients.

The large autopsy series of "Malamud and Skillicorn (N=70; [39]) and Victor and colleagues (N=245; 82 with neuropathological examination) provide much about the distribution of pathology and its correlation with clinical deficits in Wernicke-Korsakoff syndrome (WKS)" [2]. These series, gathered in California from 1946 to 1956 and in Massachusetts from 1950 to 1961, are distinguished by the breadth of their neuropathological examinations and the wealth of clinical data used to create associations. Although almost all patients had lesions in their mammary bodies, the prevalence of abscess in other periventricular locations was significantly different between the two studies (table 2). Disparities in neuropathological investigation research methods may explain these disparities in lesion occurrence. Despite exhaustive neuropathological examinations, neither report on the disease's severity or the involvement of several nuclei in a single individual. As a result of these factors, it is difficult to create a complete anatomical map of the KS clinical anomalies [2].

Table 2: Characteristics of alcoholic WKS and neuropathological findings [36]

	Malamud & Skillicorn	Victor et. al.
N	70	245
Gender (M:F)	52:18:00	154:91
"Mean Age at onset (y)	58	51
History of Alcoholism	63 (90%)	243 (99%)
Nueropathalogy (%)		
Mammiliary bodies	96	100
Dorsomedial thalamus	53	88
Pulvinar	4	85
Brainstem nuclie	23	55
Cerebellum	34	56"

Experts disagree on whether thalamic mediodorsal nucleus injury is required for KS. In two KS patients, there has been no corroboration of neuronal death in the mediodorsal nucleus or somewhere else in the thalamus. The authors established that mammillary bodies are the primary cause of sickness in KS. Mayes et al. discovered gliosis in the third ventricle but not in the thalamic mediodorsal nucleus in two cases. [40].

Diagnosis

- Korsakoff syndrome is a clinical diagnosis. A patient with thiamine deficiency should be identified with its signs and symptoms. However, waiting days for results should not delay empiric treatment.
- The Wernicke-Korsakoff syndrome is believed to have a global prevalence of 2%. Homeless, elderly, and psychiatric patients are at risk. The incidence and prevalence of Korsakoff syndrome are unknown due to underdiagnosis and disputes over diagnostic criteria [23].

Diagnosis Markers

Diagnostic sensitivity and specificity, and frequency increase in patients with unstable syndrome [41]. Three potential WKS biomarkers have been identified: CD68 positive brain tissue cells, high CSF lactate levels, and MHPG, a norepinephrine metabolite [42].

Neuroimaging

The MRI-detectable neuropathology of KS includes tissue shrinkage or atrophy in certain brain regions, such as the mammillary bodies and thalamus, as well as ventricular enlargement, which is likely due to grey matter nuclei atrophy in the surrounding area. While the hippocampus, mammillary bodies, and thalamus all have significant bilateral volume abnormalities, the medial septum/diagonal band of Broca demonstrate very minor abnormalities [43].

Initially, T2-weighted late-echo sequences were used to improve the visualisation of oedematous lesions [44]. An MRI study found that the T2 relaxation time, which indicates

axonal and myelin integrity and is a marker of interstitial fluid, has been observed to be greater in the centre brain stem of patient populations with alcoholic WKS in MRI study. [45].

The FLAIR sequence enhances the T2 method by adding T1 contrast mechanisms. FLAIR enhances signal visibility in oedematous tissue such as sulci and ventricles in *In vivo* FLAIR pictures of acute WE [46], [47]. MR diffusion-weighted imaging (DWI) is another MRI technique that is sensitive to WE brain illness because it reduces signal from freely diffusing water. Figure 5: DWI of WE lesion. The oedematous lesions of WE, which should have high diffusivity and be muted by DWI, are hyperintense.

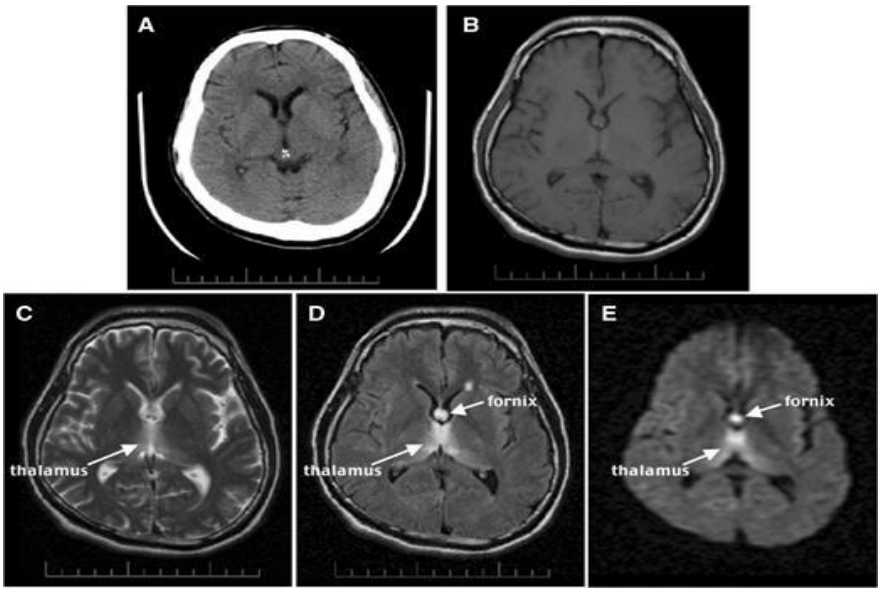

Figure 5: CT and MR scans of a 35-year-old man diagnosed with severe schizophrenia and WE caused by Vitamin B2 deficiencies.

"(A) Axial CT at the level of the lateral ventricles. (B–E) Axial MR images at a similar level to the CT. (B) A proton density-weighted image. (C) A T2-weighted late-echo fast spin echo (FSE) image. (D) A fluid-attenuated inversion recovery (FLAIR) image. (E) A diffusion-weighted image (DWI). Note the hyperintensity of the fornix and thalamus, especially in D and E, less so in C, and lack of lesion complicity in A and B [43]".

It is a case of "T2 shine-through," which occurs once tissue with a large T2 value illustrates neighboring tissue. [48]. In addition to the typical Wernicke Encephalopathy with periventricular and thalamic tissue anomalies, the cerebellum's extremely low diffusivity provided a strong signal on DWI [49], [50]. While thiamine supplementation corrected the cerebral diffusivity deficits, the motor impairment persisted [51]. In two experiments, researchers discovered higher DWI signal intensity and lower diffusivity in brain areas affected by acute WE [50], [52]. DWI is likely to be most effective when combined with ADC imaging to assess water diffusion caused by the T2 shine-through phenomena. Both methods can describe the progression of Wernicke encephalopathy lesions from edematous elevated diffusion coefficient to atrophic minimal diffusion coefficient.

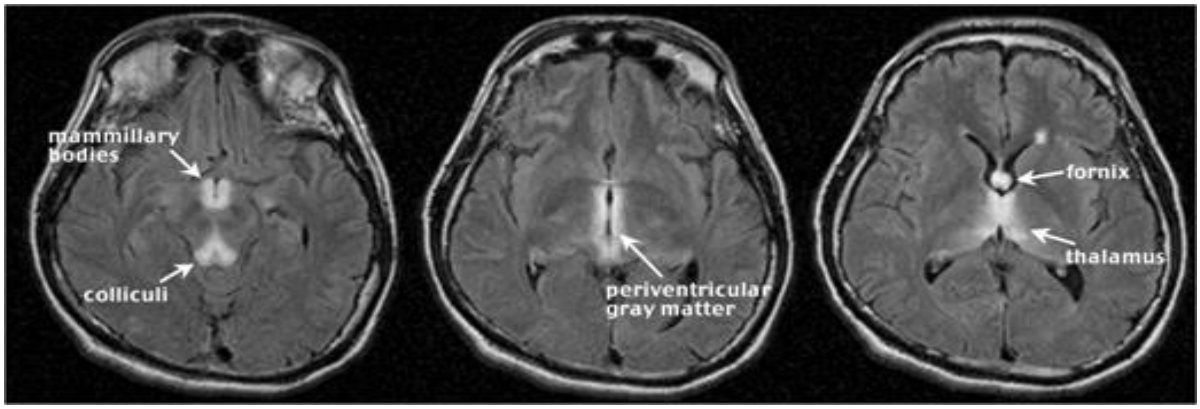

Figure 6: Three contiguous FLAIR pictures of the acute WE (5 mm thick with a 2.5 mm skip) [43].

Figures 5 and 6 are FLAIR photos of a 35-year-old man with schizophrenia who was bewildered and lethargic in his house. Malnutrition has caused people and loses weight. The treatment consisted of daily intravenous thiamine dosages of 100 mg. Attributed to the prevalence of all neuropathological markers, the abscess, in this case, is isobilateral and perceptible as signal hyperintensities.

Uncomplicated alcoholism to WKS

The neuropathology of non-WKS alcoholism must be considered in light of the degenerative changes of the brain associated with WKS. Figure 7 depicts the combined effects of persistent alcoholism, Wernicke Encephalopathy, and Korsakoff Syndrome on structural and functional brain in KS within alcoholic patients, non- alcoholism, and control participants. For volumetric estimation, some brain regions were manually identified using MRI.

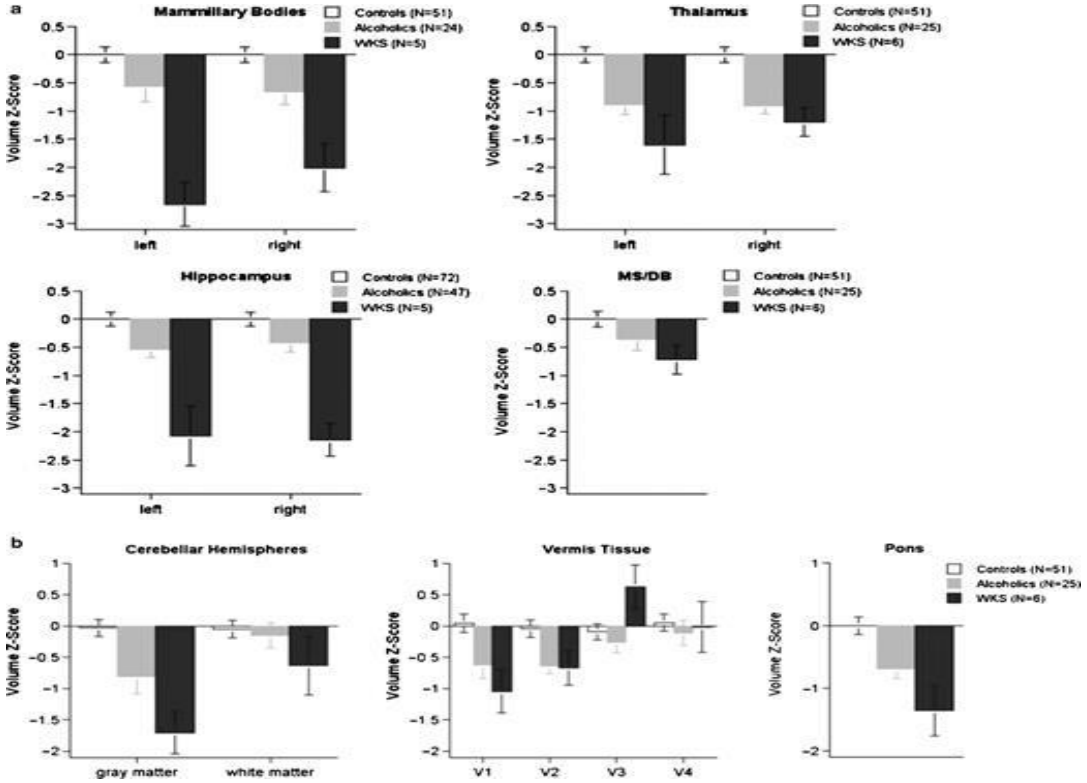

Figure 7: Alcoholism to WKS [43].

SPGR volumetric for the mammary bodies [53], thalamus [54], [55], medial septum/diagonal band (MD/DB), cerebellum [56], and pons [54], [55]; coronal, dual-e [57]. Regional brain volumes were normalized for normal intracranial volume and age variation and expressed as standardized Z-scores, with the controls' expected mean of 0 (standard deviation = 1). As a result, low scores indicate that volumes are lower than expected for a given cerebral volume and age, and mean Z-scores also represent the magnitude of the effect. Every one of the Korsakoff syndromes affected patient populations with a history of addiction to alcohol, were alcohol-free at the time of the evaluation, and encountered the Wernicke Encephalopathy retrospective chart review criteria. [58]. Neuropsychological testing revealed severe to profound abnormalities in memory for new information, gait and balance, and visuoperceptual implicit learning in the KS group, but not in short-term memory, general intelligence, or visuoperceptual implicit learning [59], [53], [50].

Alcoholics with no complications had significant deficiencies in the mammary bodies [60],[61], [59], thalamus (this study), pons (this report), cerebellar hemispheres, and anterior superior vermis (V1 of Figure 7b), but they were less severe [56]. Bilateral anterior hippocampal deficits were found in alcoholics with WKS, contrary to popular wisdom and data [62], [63], [64]. (Figure 7a). Furthermore, KS patients' hippocampus volumes were compared to those of Neurodegenerative disease (AD) patients, whose significant implication is a significant loss in hippocampal volume. [65]. The KS group had a bilateral hippocampus volume deficit similar to that of Alzheimer's patients and more than double that of non-amnesic drinkers [57].

Treatment

The majority of WKS patients develop Wernicke's encephalopathy first, followed by Korsakoff syndrome. People with KS frequently struggle to master new skills or new memories (anterograde amnesia). Unintentionally, the individual may make up information to fill up memory gaps which are referred to as confabulations. Taking thiamine supplements can reduce common symptoms such as visual anomalies, irregular eye movements, coordination problems, and confusion.

Memory and cognition deficits are less likely to improve, while urgent thiamine treatment may prevent further deterioration. Intravenous therapy is often continued until the doctor detects no improvement [66]. The treatment of Wernicke–Korsakoff syndrome with large doses of parenteral B vitamins and thiamine should be investigated as soon as possible.

Glutamatergic receptors are inhibited by alcohol, whereas GABA receptors are stimulated. The brain adjusts with time by decreasing GABA receptor activity and boosting glutamatergic receptor activity. When a chronic alcoholic stops drinking, this adaptive system is disrupted, resulting in alcohol withdrawal, a disorder that can develop to delirium tremens and convulsions in severe cases. Cortisol levels increase during alcohol withdrawal, indicating that the body is under stress [67]. Chronic alcoholism results in an increased release of glutamate due to thiamine deficiency. Together with increased glutamate receptor expression in alcoholics, this mechanism contributes to increased neurotoxicity [68]. When thiamine shortage is associated with alcohol withdrawal, the likelihood of curing the shortfall just with thiamine administration reduces. Because of cellular disturbances and nutritional deficiencies, it is vital to refrain from alcohol and follow a healthy diet [69]. The duration of

thiamine deficiency in patients undergoing alcohol withdrawal is uncertain; it varies by individual. Increased plasmatic thiamine concentration alone does not provide optimum thiamine penetration across the blood-brain barrier to participate in important enzymatic activities [70].

In Korsakoff syndrome, rehabilitation programs have a better probability of success than pharmacological therapy. Previously, it was believed that people with Korsakoff syndrome were incapable of restoring memory. However, growing evidence contradicts this idea [71].

Memory compensation strategies, such as smartwatches, smartphones, and journals, appear quite promising. Several studies investigating the use of digital technology to improve memory in patients with Korsakoff syndrome have yielded promising findings [72].

Theoretically, therapies that emphasize errorless learning should be the most appropriate for the cognitive talents and limitations associated with Korsakoff syndrome. The most important aspect of this method is that the individual is not allowed to make errors while starting to learn. All assumptions are removed to avoid a patient's procedural memory becoming accustomed to an ineffective or incorrect technique that cannot compensate for or restore a patient's impaired episodic memory. [25]. Although the outcomes of studies on errorless learning are contradictory, the benefits of this type of learning are generally favorable, and they extend beyond procedural learning to encompass semantic learning [73].

Thiamine should be given orally to the patient, and he or she should be referred for rehabilitation and treatment of any comorbid disorders. The majority of individuals with Wernicke-Korsakoff require long-term chronic care [74]. To prevent the progression of WKS, an individual must refrain from alcohol and consume a well-balanced diet. Medical therapy is essential if the problem is not caused by alcohol [66].

Brain exercise helps delay memory loss. Individuals began to exhibit symptoms of Alzheimer's disease as a result of Korsakoff syndrome, which progressed more rapidly in those who maintained an active mind. It is likely that being cognitively busy initially benefited the brain, delaying the onset of symptoms.

CONCLUSION

Thiamine deficiency is an important cause of the Korsakoff syndrome, and thiamine is a prerequisite for KS management in both alcoholics and nonalcoholics. The psychiatrist's responsibility is to improve care for these patients, organize memory rehab placements, follow-up, and thus further assessment as required. Families can be helped if they work closely with their doctors.

ACKNOWLEDGEMENT

The authors acknowledge sincere thanks to the management of GITAM Institute of Pharmacy, GITAM (Deemed to be University), Visakhapatnam, for the facilities granted for the research work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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