

Korsakoff syndrome: An overlook (Review)

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Abstract. This review aimed to analyze the latest neurobiological findings regarding Korsakoff syndrome, since alcoholism is the most prevalent addiction worldwide. In addition, we analyzed the optimal treatment that can be administered in order to minimize the symptoms and improve the outcome of these patients. The disruption of memory circuits within the brain of alcoholic patients results in the amnesic syndrome known as Korsakoff syndrome. It is generally characterized by a chronic neuropsychiatric syndrome caused by vitamin B1 (thiamine) deficiency. Other categories of patients can develop Korsakoff syndrome without consuming alcohol such as AIDS patients, terminally ill cancer patients, or patients with chronic infections and malnutrition. Vitamin B1 is required in the Krebs cycle for production of adenosine triphosphate (ATP). It is also a cofactor in the production of acetylcholine and certain neurotransmitters. Alcohol consumption can decrease the intake, gastrointestinal absorption and cellular utilization of vitamin B1. Treatment of alcohol withdrawal along with high doses of vitamin B1 can improve the general outcome of patients. A small percentage of patients can recover from Wernicke's encephalopathy with no permanent brain damage. The onset of Korsakoff syndrome darkens the prognosis. Alcohol abstinence is an absolute recommendation and prevents the extension of neural damage.

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1. Research methods

The review started from an extensive search of Korsakoff syndrome for the last 10 years over the database PubMed®/MEDLINE (<http://www.ncbi.nlm.nih.gov/pubmed>). Even if the trigger for this disease can be found in more than 2,700 scientific articles and 9 clinical trials, the Korsakoff keyword returned only 160 published scientific papers, 91 in the last 5 years and only one clinical trial. As research keywords we used 'Korsakoff' OR 'Korsakoff syndrome' OR 'Wernicke' AND 'Wernicke encephalopathy' AND 'alcohol' AND 'Thiamine' AND 'brain structures' AND 'treatment'. In the same time 'Korsakoff' search over Web of Knowledge returned 342 scientific articles but only one published in Romania. We constructed an Excel table highlighting these findings, we eliminated the duplicates, we kept the review articles because some of them bring upfront old results or ideas that are still valid and useful.

2. Introduction

Korsakoff syndrome is a chronic memory disorder that is generally preceded by an acute manifestation and illness named Wernicke's encephalopathy. The symptoms of Wernicke's encephalopathy include confusion, oculomotor disturbances and incoordination of movement especially ataxia. After an acute episode, approximately 80% of unmedicated patients develop behavioral abnormalities and memory impairments that are later diagnosed as Korsakoff syndrome.

Neuroimaging techniques performed on patients with Korsakoff syndrome demonstrate that there are specific abnormalities in the grey and white matter of alcoholic patients. Alcohol damages the structure and decreases the volume of the white matter. In alcoholic patients, there have been studies suggesting atrophy and metabolic abnormalities in the frontal lobe, amygdala, thalamus, hippocampus and cerebellum. The lesions within these brain regions involve the neurological circuits of both anterograde and retrograde memory. In severe

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2. Introduction

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cases, procedural memory and emotional processing can be affected (1).

Over time, autopsies have shown that Korsakoff syndrome is not a rare condition, especially in alcohol-abusing patients (2).

Although no clear definition of Korsakoff syndrome has been established, it is generally characterized by a chronic neuropsychiatric syndrome caused by vitamin B1 (thiamine) deficiency (3). Korsakoff syndrome occurs in those who have suffered from Wernicke encephalopathy and have not received adequate and rapid treatment with thiamine (4). This syndrome is most often associated with chronic alcohol consumption, but it can also be caused by other processes that lead to thiamine deficiency, such as malnutrition, metabolic pathologies, gastrointestinal diseases (e.g. Crohn's disease or pancreatitis), hyperemesis gravidarum, HIV, infections, and anorexia nervosa (5). Its effects can be observed after bariatric surgery; thus, supplementation of the diet with vitamin B1 is required in order to achieve adequate prevention (3).

Patients who develop Korsakoff syndrome for reasons other than alcohol use are mostly women and young patients. Unlike alcoholic patients who develop Korsakoff syndrome, non-alcoholic patients exhibit better survival and higher cure rates (6). Korsakoff syndrome is in the same family as Wernicke's encephalopathy, but a major difference is that Wernicke's encephalopathy is acute and often reversible, and Korsakoff syndrome is chronic and often irreversible (7).

When the two pathological entities (Wernicke's encephalopathy and Korsakoff syndrome) present together, it is stated that the patient suffers from Wernicke-Korsakoff syndrome. Wernicke's encephalopathy is characterized by acute confusion, while Korsakoff syndrome is characterized by confusion, memory disorders and gait abnormalities (4,7).

Research concerning Korsakoff syndrome have made a great contribution and a better definition of the concepts of memory; and moreover, have indicated that the structures of the diencephalon play a crucial role in memory (4).

Thiamine has been the first-line treatment for more than 50 years, but there are still some uncertainties about the dose and duration of treatment (2).

3. Clinical features

It is often difficult to differentiate Wernicke's encephalopathy from Korsakoff syndrome because both belong to the same spectrum of disease, with their etiology consisting of thiamine deficiency. Doctors must screen for both pathologies when certain clinical features are present (8).

Normally, Wernicke's encephalopathy is unraveled by the triad ataxia, ophthalmoplegia and altered mental status. Few patients present all of these criteria. Signs and symptoms that may be associated with Wernicke-Korsakoff syndrome are ataxia, oculomotor disorders, and impaired mental status (8). Thiamine is a cofactor for several enzymes and can be involved in the propagation of action potential along the axon and in the synaptic transmission (9).

There are certain cognitive disorders specific to Korsakoff syndrome, such as anterograde and retrograde amnesia, limited learning ability, and deficits in executive function. These deficits lead to impaired judgement, planning, problem solving and decreased inhibition of the central nervous system (10).

Caine criteria have been developed to diagnose Wernicke's encephalopathy, but due to the frequent overlap with Korsakoff syndrome, they can also be used to diagnose Korsakoff syndrome (11). In order to diagnose Wernicke's encephalopathy at least two of the following signs must be present: Oculomotor disorders, cerebellar dysfunction, nutritional deficiency, altered mental status or mild memory disorder (8).

Although Korsakoff syndrome is defined as a memory disorder, it is obvious that it contains multiple behavioral and cognitive symptoms. As reported in review articles, in addition to amnesia, Bonhoeffer and Gudden also specified blunt affect, confabulations and apathy as characteristic symptoms (4,12).

Memory disorder is the most studied symptom of Korsakoff syndrome. Patients have trouble with episodic memory (13), but also with spatial, contextual and other types of memory (14,15).

The diagnosis of Korsakoff syndrome is made based on mainly clinical symptoms, in addition to laboratory and imaging tests. Doctors often have to deliberate about the possibility of this diagnosis because it is easy to be missed and because delaying treatment greatly increases mortality. Even if the diagnosis has not been confirmed, it is relatively safe to administer thiamine prophylactically. Thiamine should be administered before glucose to avoid the onset of Wernicke-Korsakoff syndrome (16,17).

4. Neurobiology

The neurobiology of Korsakoff syndrome is closely linked to the direct neurotoxic effects of alcohol. The neuropathological findings regarding Korsakoff syndrome conclude that chronic alcoholism can disrupt neural pathways at both macroscopically and microscopical level. Postmortem studies have confirmed that the brain of alcoholic patients consists of multiple site atrophy, especially in the frontal lobes, limbic system, the hypothalamus and cerebellum (18). These regions are the most vulnerable of being damaged by alcohol.

The frontal lobe, especially the prefrontal cortex, is the center of our personality and executive abilities. In addition, this region of the brain connects to multiple association areas, thus being at the root of our logical thinking and understanding of the world. Disruption of this circuitry due to atrophy and direct neurotoxicity causes episodic and executive memory loss, along with personality and emotional processing changes (19,20).

Patients with impaired frontal lobe activity due to alcoholism or Korsakoff syndrome tend to be more impulsive and aggressive. There are multiple explanations for their inability to control their impulses (21). In some cases, a premorbid personality can lead to alcoholism, such as an antisocial personality disorder (22). Other studies suggest that disruptions in the normal inhibitory functions of prefrontal networks can lead to the manifestation of behavioral inhibition (23).

The limbic system is an integrating part of the body's homeostasis, and facilitates memory, learning and behavioral responses. The hippocampus is part of the limbic system and is one of the key brain regions that modulate the recollection of memory. Subsequently, it is one of the few regions in the brain that have neurogenesis properties. Studies measuring the volume of this region suggest that alcohol can interfere and

decrease the neurogenesis in the hippocampus (24). The hypothalamus is part of the learning neural network. Prolonged exposure to alcohol can damage the mammillary bodies that are a specific region of the hypothalamus controlling learning and recollection of memory. Patients with Korsakoff syndrome that present destruction of the mammillary bodies have amnesia and are unable to form new memories (25).

The cerebellum is a brain region that has been associated with motor skills. Recent studies suggest the involvement of the cerebellum in cognition (25). Cerebellar atrophy is highly associated with alcoholism. Studies have observed that total volume shrinkage of the cerebellum in alcoholic patients is correlated with different executive tests, suggesting the importance of the frontocerebellar circuitry (25).

As discussed previously, we stated that the majority of patients with Korsakoff syndrome undergo an acute manifestation named Wernicke's encephalopathy. Studies conclude that there is a continuum from cognitive intact alcoholic patients to Korsakoff syndrome (26). The pattern of grey and white matter damage is similar in alcoholic patients and Korsakoff syndrome patients, the difference being that the latter diagnosis consists of more neurobiological damage in key areas of the brain (27).

5. Treatment strategies

The treatment of Korsakoff syndrome is hampered by two major unsolved questions. Is thiamine effective in preventing and treating Korsakoff syndrome? What is the optimal form, dose and duration of thiamine treatment in this syndrome? (4,27).

Alcohol interacts with multiple neurotransmission pathways, such as the γ -aminobutyric acid (GABA) pathway and the glutamatergic system, thus being a nonspecific drug. The action on these receptors leads in time to the development of tolerance and dependence. Alcohol inhibits glutamatergic receptors and stimulates GABA receptors. Over time, the brain adapts by reducing the function of GABA receptors and increasing the function of glutamatergic receptors. When a chronic alcohol user stops drinking, this adaptive system is disrupted and alcohol withdrawal occurs, a pathology that leads in extreme cases to delirium tremens and seizures. During alcohol withdrawal, an increased amount of cortisol is released, which translates to a stressful event within the body (28).

The thiamine deficiency that occurs in chronic alcoholism leads to excessive release of glutamate. This mechanism along with the upregulation of glutamate receptors in alcoholic patients determines increased neurotoxicity (29).

If thiamine deficiency is associated with alcohol withdrawal, the chances of this deficiency being eliminated only by thiamine administration are reduced. Due to cellular disturbances and nutritional deficiencies, abstinence from alcohol and optimal nutrition are necessary (30).

It is not clear how long thiamine deficiency persists in ethanol withdrawal; it varies depending on the patient. Higher plasmatic concentration of thiamine does not guarantee the optimal penetration of the brain-blood barrier in order to participate in the required enzymatic processes (31).

Often, patients with Korsakoff syndrome have permanent or semi-permanent brain damage when they are admitted to the hospital. As in most diseases, the best treatment is prophylaxis;

thus, patients at risk should be identified and treated with an adequate amount of parenteral thiamine. Early intervention is essential, as it is most effective when carried out before brain changes occur.

In the past, it has been suggested that there is a difference between Korsakoff syndrome due to nutritional deficiencies and Korsakoff syndrome due to nutritional deficiencies and alcohol consumption. There is a hypothesis that in the case of patients who only consume alcohol, the mechanism of thiamine deficiency is different and it requires higher doses of thiamine (31).

It is extremely important to consider that the cure for Korsakoff syndrome is not only related to the amount of thiamine, but also to other enzymes, as well as the transport of thiamine at the neuronal level. The reality is that the majority of chronic alcoholics develop Korsakoff syndrome even when they are administered thiamine at the time that they develop Wernicke's encephalopathy (31).

The response to parenteral thiamine is variable. Some patients require high doses of thiamine, over 1 g parenterally on the first day, while others respond to low doses. Although thiamine supplementation theoretically allows neurons to function efficiently, this does not always occur as there are often other nutritional deficiencies, such as magnesium or folate (4).

In Korsakoff syndrome, the prospects for rehabilitation programs are more promising than for pharmacological interventions. A previous theory stated that it is impossible for patients with Korsakoff syndrome to recover memory, but there is more and more evidence that contradicts this theory (32).

Memory compensation techniques such as the use of smartwatches, telephones and diaries are quite promising. Several studies that have measured the use of digital technologies to assist memory in patients with Korsakoff syndrome have shown favorable results in this regard (33).

Interventions based on errorless learning are theoretically best-suited for cognitive abilities and disabilities in Korsakoff syndrome. Its most important element is that the patient is not allowed to make mistakes during learning. All assumptions are removed so that the procedural memory of a patient cannot become familiar with an incorrect or unproductive strategy, which defective episodic memory cannot correct or compensate for (10). The results of studies for errorless learning are mixed, but they tend to be favorable for this type of learning, and the benefits do not stop at procedural learning, but also support semantic learning (34).

Patients who have been consuming ethanol for a long time are often underweight, so in addition to other nutritional principles, they also require glucose. Thiamine is needed to use glucose in the body. From these notions, it can be inferred that by overloading a patient who has a thiamine deficiency with glucose might facilitate the development of Wernicke's encephalopathy. These patients require parenteral administration of vitamins from the B complex before they receive glucose (35).

A general indication is that all patients undergoing an alcohol detoxification process should receive parenteral thiamine as a prophylaxis for Wernicke-Korsakoff syndrome. There are no solid studies yet to determine the best dose, frequency and duration of use. Expert guidelines are for patients to receive

250 mg/dose for 5 days intravenously, followed by thiamine or oral B vitamin complex for as long as needed (36,37).

Vitamin B1 products administered intramuscularly have a lower incidence of anaphylactic reactions than intravenously delivered products. The products with the lowest risk of anaphylactic shock are the ones that are administered per os (orally). Given the risk-benefit ratio, parenteral administration of vitamin B1 is more advantageous.

In 1993, a case was reported of a 37-year-old individual who survived a suicide attempt. It was observed after the suicide that the person was suffering from amnesia, dementia, apathy and behavioral abnormalities. A diagnosis of hypoxic brain damage was attempted, but only after six years, at autopsy, extensive pseudo-systematic thalamic degeneration and atrophy of the mammary body was discovered, thus indicating a Wernicke-Korsakoff post-syndrome status. Therefore, the precipitation of the disease is attributed to the synergistic effect of hypoxia/cerebral ischemia and thiamine deficiency (38). In general, these patients exhibit spontaneous affective behavior and demonstrate emotional passivity, which is often confused with clinical depression.

As mentioned previously, Korsakoff syndrome is an amnesic disorder usually associated with chronic alcohol consumption. Although the most prevalent disorder is post-traumatic stress disorder, the chances of a person with alcoholism suffering from a major depressive disorder are higher than in the general population (39). In a study by Swendsen *et al*, the researchers observed, in different cultural communities, a significant comorbidity between alcoholism and anxiety and depressive disorders. Although there appears to be a lifetime prevalence of these disorders, people with alcoholism are two to three times more likely to develop anxiety or depressive disorders (40).

At the neurobiological level, regarding the pathophysiology of alcoholism and major depressive disorder, an alteration in glutamatergic neurotransmission in the prefrontal cortex could be a contributing factor. Immunoreactivity to excitatory amino acid transporter 2 (EAAT2) appears to be lower in individuals with major depressive disorder and those with alcoholism. These results suggest that there are changes in the expression of glial glutamatergic markers in depression and alcoholism and a reduction in some aspects of glutamatergic processing in depression (41).

Although studies support the relationship between alcoholism and major depressive disorder, the causal chain is not clear. We can speculate that some depressed people may use alcohol as a maladaptive coping mechanism to cope with the symptoms, thus developing an alcohol disorder. In combination with low self-care, excessive alcohol consumption and poor diet may be predisposing factors for the development of Korsakoff syndrome.

It has been postulated that cerebello-cerebral disconnection may play a role in Korsakoff syndrome memory and executive dysfunction (42). Fewer Purkinje cerebellar cells compared to normal controls have been demonstrated in alcoholics (43), including those with Wernicke-Korsakoff syndrome (44). Although in this study the cases of Korsakoff were not analyzed separately, the marked loss of Purkinje cells in thiamine-deficient alcoholics with signs of mental status (44) adds support to the hypothesis that disruption of cerebello-cerebral

pathways could contribute to neurocognitive dysfunction in Korsakoff. However, the relative contributions of thiamine deficiency and alcoholism remain to be fully elucidated.

6. Conclusions

The etiology of Korsakoff syndrome is mainly due to chronic alcohol consumption. Alcohol abuse can trigger a cascade of biochemical reactions that target specific regions of the brain that are more susceptible to damage. The exact reason why those brain regions are targeted is still not fully understood. In order to prevent neurotoxicity, high concentrations of vitamin B1 can be administered and the consumption of alcohol must be discontinued.

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Authors' contributions

ST and IP designed and drafted the initial review. IR and AMD gathered the medical information and conducted the final view and structure of the article and investigated the present area of research and gathered the important information. IR and MBC finalized the work and analysis of the results and ST approved the final version of the review. All authors read and approved the final manuscript for publication.

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Competing interests

The authors declare that they have no competing interests.

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