Wernicke-Korsakoff Syndrome Pathophysiology in Alcoholics

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Introduction

Wernicke-Korsakoff Syndrome (WKS) (Figure 1) is a neuropsychiatric disorder caused by deficiency of thiamine (or vitamin B1), which is predominantly observed in individuals with a higher intake of alcohol.

Two hypotheses non-exclusive explain the damage in the central nervous system (CNS) in alcoholics developing WKS (Figure 2).

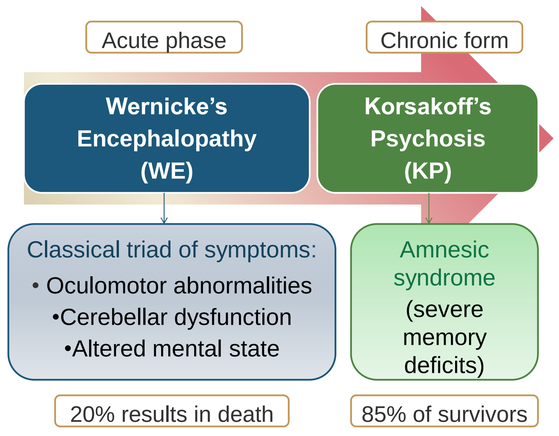

Figure 1. WKS comprehends an acute phase (WE) and a chronic form (KP).

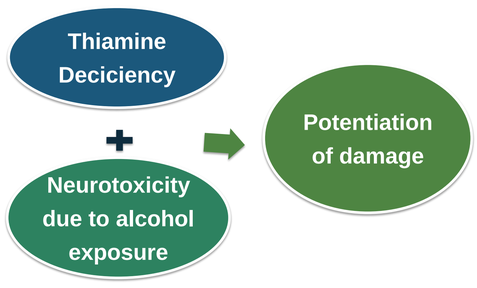

Figure 2. The combination of both factors leads to a synergic effect for the severity of brain damage.

Studies from autopsies revealed that the disorder is still greatly underdiagnosed. Then, clinical considerations for proper diagnosis and treatment are also going to be discussed.

Pathophysiology of Thiamine Deficiency Alone in CNS

The biologic active form of thiamine (Figure 3) acts as a cofactor for three apoenzymes directly implicated in the metabolism of glucose (Figure 4).

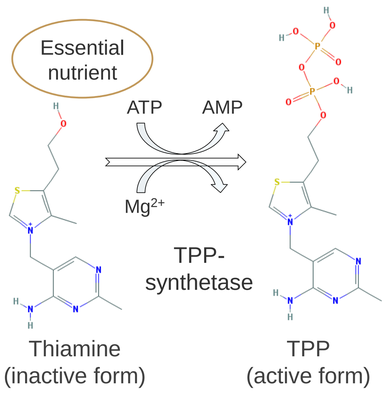

Figure 3. In humans, thiamine must be obtained from an exogenous source; for its activation in enterocytes thiamine pyrophosphate (TPP)-synthetase is required, which transfers the pyrophosphate group from ATP to the thiamine.

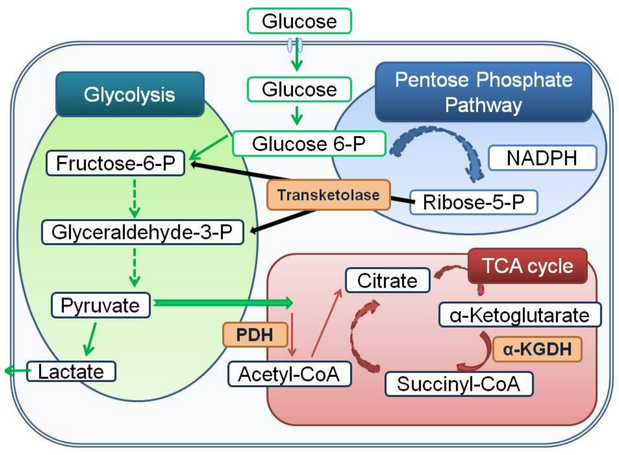

Figure 4. The three thiamine-dependent enzymes are transketolase (in pentose phosphate pathway), pyruvate dehydrogenase (PDH) (connecting glycolisis with tricarboxilic acid -TCA- cycle), and α-ketoglutarate dehydrogenase (α-KGDH) (in mitochondrial TCA cycle)

Various mechanisms through thiamine deficiency can lead to cell damage in CNS (Figure 5):

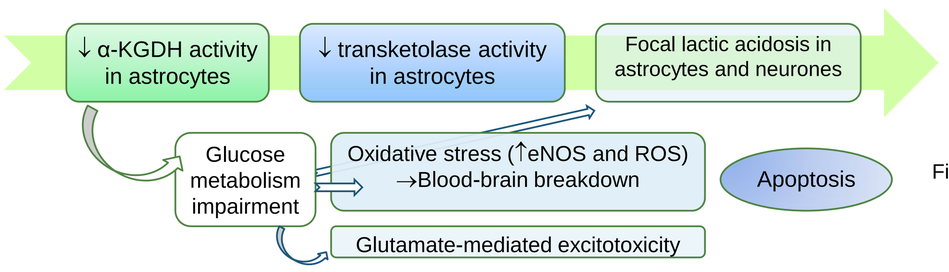

Figure 5. Alterations due to thiamine deficiency

Pathophysiology of Chronic Alcohol Exposure in CNS

Ethanol enhances $GABA_A$ receptors and inhibits NMDA receptors (Figure 6).

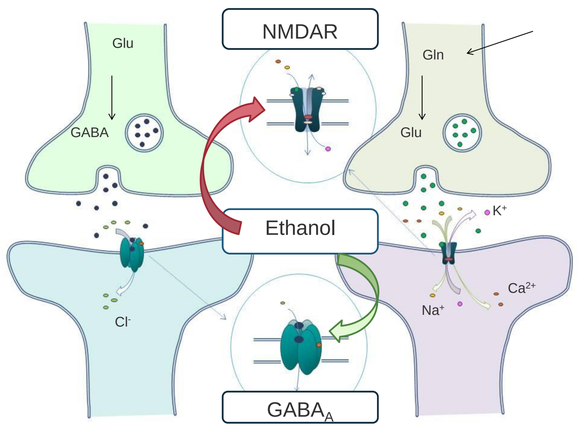

Figure 6. Alcohol interacts with the GABA and *N*-metyl-*D*-aspartic acid (NMDA) systems. The structure of receptors involved are also represented.

Chronic alcohol consumption leads to neuroadaptative compensatory mechanisms:

↑NMDAR expression

$GABA_A$ structure modification

Repeated episodes of drinking and withdrawal results in glutamate-induced excitotoxicity and lasting neuronal damage (Figure 7). Moreover, the potential for neurotoxicity increases during withdrawal periods.

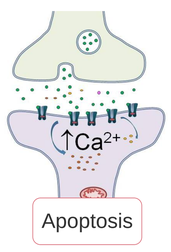

Figure 7. Overactivation of NMDAR results in high influx of Ca^{2+} into the cell , which compromises mitochondrial function and causes DNA damage, lasting in apoptosis of the cells.

Thiamine Deficiency in Alcoholic Brain

80% of cases of thiamine deficiency

In alcoholics with WKS, the combination of thiamine deficiency and alcohol consume leads to a synergic effect for damage in CNS (Figure 8).

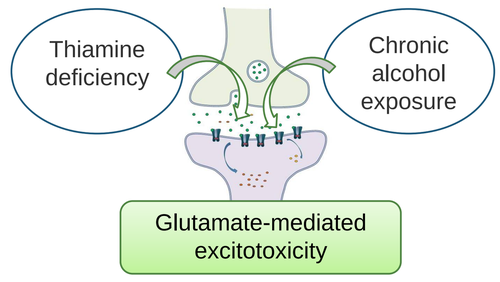

Figure 8. Excitotoxicity caused either by alcohol exposure and thiamine deficiency results in an increase of damage potential when both are combimed

1,4 mg of thiamine per day

It is the recommended dose for a healthy adult (but ↑ in alcoholics)

Furthermore, some factors affect the thiamine availability in the brain in abusive alcohol consumers (Fig 9):

Inadequate thiamine intake	• Unbalanced nutrition • Loss though vomits, diarrhoea, steatorrhoea
Impaired transport of thiamine	• Interference with active transport • Reduced thiamine phosphorilation
Other nutritional deficiencies	• Magnesium deficiency (cofactor for transketolase and TPP) • Folate, vitamin B6 and B12
Organ damage	• Liver damage
Genetic predisposition	• Thiamine-dependent enzymes, GABA receptors • Cellular transport carriers: THTR-1 and THTR-2
Inadequate treatment	• Low or insufficient doses of thiamine (oral or parenteral)

Figure 9. Mechanisms through alcohol consume could increases the demand for thiamine.

Clinical Considerations for Diagnosis and Treatment of WKS

Post-mortem findings indicate that prevalence of WKS in alcoholics is higher than appreciated. Non-recognition of patients with WKS is probably due to the fact that most of them only exhibit only one or two classic symptoms of the triad (Figure 10).

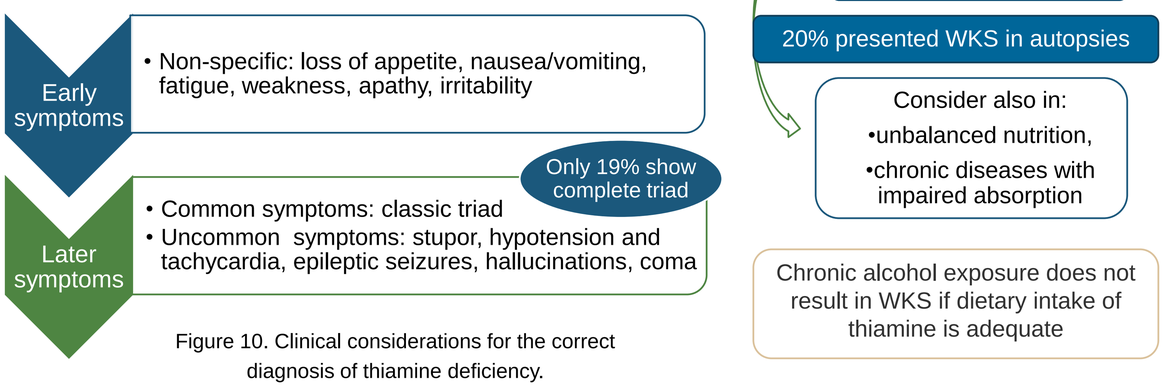

Figure 10. Clinical considerations for the correct diagnosis of thiamine deficiency.

Those alcoholic individuals suspected of suffering WE should be treated with parenteral thiamine since treatment with oral thiamine is ineffective (Figure 11). Nevertheless, the optimal treatment strategies for WKS still remain in dispute.

Thiamine Deficiency Alone	Alcoholics with signs of WKS
• Oral thiamine	• Parenteral thiamine

Figure 11. Clinical considerations for the treatment of WKS

Conclusions

- WKS lesions in CNS result more severe in alcoholic patients, due to the synergic effect when thiamine deficiency and alcohol exposure are combined.
- Alcohol consume contributes to thiamine deficiency through different mechanisms, which increases the risk of developing WKS.
- Most alcoholics with WKS prior to death are underdiagnosed, then clinical considerations are needed for the proper diagnosis.
- Further work is needed to optimize the treatment of WE and to prevent the progression to KS.

Bibliography

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