# THE ROLE OF B-VITAMINS IN NEUROLOGY

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S u m m a r y. B-vitamins are group of water-soluble molecules, essential for metabolic processes. They are coenzymes and have pivotal role in correct functioning of the organism. The aim of this article is to present the role of B-vitamins in neurological diseases. Their deficits can have a significant impact on the nervous tissue. Neurological symptoms due to cobalamin deficit result from demyelination of the spinal nerves. Reduced activities of thiamine-dependent enzymes was found in many neurodegenerative diseases, including Wernicke-Korsakoff encephalopathy, Parkinson's disease, Huntington's disease, Alzheimer's disease, as well as in paralytic syndromes. Other vitamins, whose deficit accounts for neurological disorders include vitamin B2 and B6. Studies that provide evidence for the role of B vitamins in the pathogenesis of neurodegenerative changes create an opportunity to develop new treatment strategies using vitamins.
K e y w o r d s: B-vitamins, cobalamin, thiamine, neurology.

## INTRODUCTION

B-vitamins are group of water-soluble molecules, which play very important roles in metabolism. They are coenzymes and have pivotal role in correct functioning of the organism. Their collective effects are particularly important for the brain function, DNA/RNA synthesis or repair, methylation, energy production, and the synthesis of neurochemicals and signaling molecules [1]. Thiamine (vitamin B1), riboflavin (vitamin B2), and cobalamin (vitamin B12) are the most important for the proper function of the nervous system [1, 2]. Their deficiency can have a comprehensive impact on functioning of the nervous tissue. It can cause a group of neurological diseases such as Wernicke Encephalopathy, Korsakoff syndrome, Parkinson's disease, subacute conditions combined with the spinal cord degeneration [3]. It is proved, that deficiency of these vitamins affects the course of diseases such as multiple sclerosis, stroke, dementia, and Alzheimer's disease [4, 6].

## MATERIALS, METHODS, AIM

The aim of this article is to present the role of B-vitamins in neurological diseases. Standard criteria were used to review the literature data. We reviewed articles written in English, mainly in the PubMed database using the following keywords such as B-vitamins, thiamine, riboflavin, cobalamin, neurology, and neurological diseases. Only full-length scientific articles published in peer-reviewed journals were considered.

## RESULTS

Thiamine (vitamin B1) together with riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), pyridoxine and its derivatives (vitamin B6), biotin (vitamin B7), folic acid (vitamin B9) and cobalamin (vitamin B12) belong to B-vitamins [6]. Vitamins from this group differ in chemical structure and specific functions, but they also have several common properties. All of them are soluble in water, they are exogenous compounds, and must be supplied with food [7].

## B12 vitamin in neurological diseases

Vitamin B12, also known as cobalamin is a cofactor of enzymes in many processes, e.g. DNA synthesis, fatty acid, citric acid cycle and amino acid metabolism, especially in homocysteine convertion to methionine [8, 9]. This vitamin has a comprehensive impact on the body, and is particularly involved in normal functioning of the nervous tissue like synthesis of myelin, or protection against neuronal degeneration by superoxides [9, 10]. Vitamin B12 is also crucial for red blood cells production [11].

The deficiency of vitamin B12 has significant neurological consequences. Cobalamin deficiency can cause subacute combined degeneration (Lichtheim's disease) which affects the dorsal and lateral columns of the spinal cord [12]. It leads to abnormal myelination or demyelination, resulting in combined degeneration, peripheral neuropathy and psychiatric problems such as depression, dementia, delusions. Vitamin B12 deficiency also leads to brain shrinkage and neurodegeneration [13].

B12 with folic acid can reduce the risk of stroke and blood homocysteine level. Lower levels of B12 and folic acid were correlated with higher level of homocysteine [11, 14]. According to Spence (2006), hyperhomocysteinaemia has an impact on developing atherosclerosis. B12 deficiency was observed in 10% patients under 50 with stroke or transient ischemic attack, 13% aged 50-70, and 30% patients over 70 [5]. Moreover, according to Zhihong Shi et al. patients with the highest homocysteine levels (>18.6 μmol/L) had a 1.61-fold increased risk of death compared with patients with the lowest levels (≤10 μmol/L). This correlation was only significant in the large-artery atherosclerosis stroke subtype [15]. Supplementation of this vitamin should be implemented in case of deficiency in patients with risk factors of stroke [16].

Deficiency of B12 can also cause epileptic-like seizures. According to case report of Lubana et al. new onset of generalized tonic-clonic seizures was correlated with low level of cobalamin. There were no other potential causes. After B12 supplementation seizure attacks disappeared [13].

The activity of B12 is significant in the course of Multiple Sclerosis (MS), which affects the age of the disease onset, duration, and subtypes, however disability status is unclear. According to Vrethem et al., both vitamin B12 deficiency and MS can have similiar symptoms [17]. According to Najafi et al., Goodkin et al. and Vrethem et al., no assocation between B12 level and MS, age of the disease onset and clinical disability was found [17, 18, 19]. On the other hand, some research proved that vitamin B12 deficiency and concomitant hyperhomocysteinaemia could aggravate MS [20]. Furthermore, according to Kocer et al., vitamin B12 deficiency can lead to prolonged visual evoked potentials (VEP) and posterior tibial somatosensory evoked potentials (SEP) [21]. Higher level of homocysteine can be involved in the development of depression and prolonged posterior tibial SEP in patients with MS [5]. The role of Vitamin B12 in MS is uncertain and therefore requires further research [22].

## B1 vitamin in neurological diseases

Three forms of thiamine are found in the human body, i.e. thiamine monophosphate (TMP), thiamine pyrophosphate (TDP) and thiamine triphosphate (TTP) [23]. However, TDP is the only biologically active form [24]. Thiamine pyrophosphate plays a very important role in energy metabolism in the nerve cells, because it participates in the conversion of pyruvate to acetyl-CoA. TDP functions as a coenzyme of the enzymes involved in the oxidation of α-ketoacids in the Krebs cycle. It also takes part in the synthesis of ribose, necessary for the synthesis of nucleic acids [25]. In the cytoplasm of cells, TDP is a cofactor of transketolase, a pentose monophosphate cycle enzyme that provides NAPDH for the synthesis of fatty acids, as well as for the synthesis of glutathione [26]. Maintaining proper level of glutathione in the brain is particularly important due to the high production of free radicals. In addition, vitamin B1 is involved in myelogenesis, axonal growth and synapse formation [27]. It affects signal transmission in the nervous tissue, and participates in its repair.

Reduced activity of thiamine-dependent enzymes was found in many neurodegenerative diseases, including Wernicke-Korsakoff encephalopathy, Parkinson's disease, Huntington's disease, Alzheimer's disease, as well as in paralytic syndromes. It confirms the existence of a relationship between thiamine concentration and the progress of neurodegeneration [28]. As a result of long term studies, the brain areas susceptible to degeneration due to thiamine deficiency were identified, i.e. the thalamus, cerebellum, brain stem, and the mammillary body [29].

Recent reports indicate a strong relationship between thiamine and Parkinson's disease (PD) [30]. The correlation between the symptoms and low blood plasma vitamin B1 levels indicates that its supplementation may have a positive effect on the disease course. In the cases where treatment of PD was supplemented with thiamine, reduction of dyskinesis and parkinsonism symptoms was observed [31]. Luong et al. showed that the daily dose of thiamine 100-200 mg significantly improved motor function of patients with PD [32].

Disturbed energy metabolism due to deficiency of thiamine pyrophosphate contributes to the development of Wernicke-Korsakoff syndrome. The first acute phase of the disease is usually reversible after the administration of vitamin B1. However, with a longer course, it goes into an irreversible phase in which, the areas of the cerebral cortex responsible for memory consolidation are destroyed [33].

Studies on animal models show that disorders of thiamine-dependent processes are the cause of pathological changes in Alzheimer's disease (AD) [34]. Reduced activity of energy metabolizing enzymes accelerates amyloidogenic conversion of APP protein which suggests that the administration of thiamine to patients with AD may bring a beneficial therapeutic effect. However, this dependence requires further research.

According to Gruber et al. low levels of thiamine and the decrease in glutathione synthesis intensify the effects of oxidative stress and neurodegenerative processes in Huntington's disease (HD) [35].

**Other B-vitamins in medicine**

Vitamin B2 is the precursor of two coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Both forms take part in the oxidation-reduction processes. Researchers suggest that riboflavin may have a significant association with childhood neuronanopathy [36]. The group of these diseases also includes Brown-Vialetto-Van Laere syndrome (BVVL), which is the result of a mutation in *SLC52A2* gene that encodes RFVT2 riboflavin transporter. Forman et al. (2018) published the results of their study, in which they showed that oral administration of high riboflavin doses to children with BVVL syndrome improved clinical and biochemical symptoms [37]. Positive therapeutic effect after riboflavin supplementation in children with BVVL was also reported by Rizzo et al. and Thulasi et al. in two independent studies [38, 39]. *AIFM1* gene codes mitochondrial flavoprotein that uses riboflavin as a cofactor. Mutations within *AIFM1* cause severe infant cerebellum ataxia, which may be accompanied by auditory neuropathy, ophthalmoplegia, axonal neuropathy and hyporeflex. According to Heimer et al. the ataxia of the cerebellum caused by *AIFM1* mutation may be cured partially with high doses of riboflavin [40]. A few studies suggest that vitamin B2 is a safe and well-tolerated option in the prevention of migraine symptoms [41, 42]. However, there is not enough evidence to recommend the use of vitamin B2 as a supportive therapy for people with migraine.

Vitamin B6 is a group of 6 chemical compounds, derivatives of pyridine. Pyridoxal-phosphate (PLP) is its biologically active form produced *via* the conversion of pyridoxine by pyridoxamine 5'-phosphate oxidase [43]. PLP is a cofactor of over 100 enzymes that catalyze reactions in the central nervous system. It participates in neurotransmission, phosphorylation of glycogen, and is involved in the expression of many genes. Disturbed activity of this vitamin contributes to various neurological disorders. PLP deficiency is involved in epileptic encephalopathy. Pyridoxine-dependent epilepsy (PDE) in newborns and infants is a type of genetic epilepsy (autosomal, recessive) [44]. They are characterized by persistent epileptic fits that do not respond to standard antiepileptic treatment, but disappear after the administration of therapeutic doses of pyridoxine or pyridoxal phosphate [45]. Guerriero et al. demonstrated that PLP deficiency is involved not only in the pathogenesis of epilepsy, but also in a series of neurological and systemic symptoms, especially in newborns [46]. Among the examined children with PLP deficiency, movement disorders, developmental delay as well as retinopathy, anemia, and inability to develop were observed. Too small amounts of vitamin B6 are also a risk factor for the occurrence of dementia. PLP deficiency in plasma is associated with decreased cognitive ability and depression. In the Smith's study among older people with mild cognitive impairment, daily supplementation of vitamin B6 (20 mg) for 24 months markedly decreased (by more than 50%) and slowed brain atrophy compared to the placebo group [47].

Vitamin B9 positively affects the nervous system and the brain [48 ]. The results of the research prove that deficiencies of B-vitamins have an important role in therapy. Other B-vitamins, such as vitamin B3, B5, B7, and B9 are also essen-

tial for health [6]. The characteristics of B-vitamins are presented in the Table 1.

Table 1. Characteristics and differences between B-vitamins [8, 9, 25, 43, 48, 49, 50, 51, own elaboration].

| Name of Vitamin | Role in the body | Food sources of vitamin | Recommended daily amount |
|---|---|---|---|
| Thiamine (vitamin B1) | It is a coenzyme of the enzymes involved in α-ketoacids oxidation in the Krebs cycle; takes part in the synthesis of ribose. | seeds, meat, eggs, whole grains, milk | 2 mg |
| Riboflavin (vitamin B2) | It takes part in the oxidation-reduction processes. | whole grains, meat, seeds, nuts | 1.5 mg |
| Niacin (vitamin B3) | It takes part in the synthesis and distribution of carbohydrates, fatty acids and amino acids, in metabolic processes aimed at energy release. | eggs, meat, fish, legumes, fruit | 14-16 mg |
| Pantothenic acid (vitamin B5) | It is essential for the proper metabolism of proteins, sugars and fats and for the synthesis of certain hormones. | meat, vegetables, legumes | 7 mg |
| Pirydoxine (vitamin B6) | It participates in neurotransmission; participates in phosphorylation of glycogen; plays a role in the expression of many genes. | meat, milk, whole grains, potatoes | 2 mg |
| Biotin (vitamin B7) | It takes part in gluconeogenesis, fatty acid synthesis, and the citric acid cycle. | meat, eggs, nuts, cereals | 30 μg |
| Folic acid (vitamin B9) | It regulates the growth and functioning of cells; positively affects the nervous system and the brain. | vegetables, meat, egg, fruit, milk | 400 μg |
| Cobalamin (vitamin B12) | Production of red blood cells; Synthesis of DNA and RNA; proper functioning of neurons. | meat, fish, egg yolk, cheese | 2.4 μg |

## DISCUSSION

Nutrition is important for mental health, it affects the development of the brain and its functioning. The results of the research prove that deficiency of B-vitamins is important in the pathogenesis of neurological disorders. The effect of their supplementation in the potential treatment of some neurodegenerative diseases is also significant. Vitamin B12 is crucial for proper function of the nervous system. The majority of people with cobalamin deficiency are the elderly [52], with the incidence about 10-20% among seniors. Neurological symptoms of low level of this vitamin are associated with the demyeliniation of the spinal nerves. Common diseases include polyneuropathy, subacute combined degeneration of the spinal cord, which can cause paresthesia and sensation disorders. Specific for cobalamin deficiency is Lhermitte's sign [53], which can sometimes be the first symptom of low B12 level. Low level of this vitamin can also trigger seizures. Vitamin B12 is known as a scavenger of superoxide molecules, that is why its deficiency can cause atrophy of the optic nerves and blindess. B12 vitamin is also important in the prevention of stroke due to its potential to decrease homocysteine level. Controversial is the correlation between B12 deficiency and the course and severity of multiple sclerosis. Some research reports indicate cobalamin deficiency as worsening the course of MS, others prove that low level of B12 does not have negative impact on MS. This subject is unclear and requires futher research [7-22]. Vitamin B1 affects many systems of the body, especially the nervous system. Because the vitamin is not stored in the body, the symptoms of its deficiency appear very quickly. Chronic deficit contributes to the development of neurodegenerative diseases, due to its important role in the nerve tissues. In addition, research shows that the supplementation with thiamine may be neuroprotective, preventing the development of neurological disorders. Also, the supply of vitamin B1 may have a positive effect on the course of advanced neurodegenerative conditions, through the potentialization of treatment [27]. Determination of thiamine concentration in the blood of patients may be a useful marker that indirectly indicates the possibility of brain damage and the development of neurogenic changes in many diseases.

There are also other vitamins important in neurological diseases. Vitamin D is mainly associated with calcium metabolism. However, its low level in the plasma may cause neuronal degeneration and cognitive loss. Numerous studies have confirmed the relationship between decreased levels of vitamin D in the blood and the occurrence of dementia [54]. French scientists conducting a study involving over 5,000 women have proven that the degree of impairment is associated with low dietary intake of vitamin D [55]. Vitamin D levels are lower in MS patients compared to healthy persons. High levels of vitamin D was associated with high chance of remaining relapse-free in the patients with relapsing-remitting MS [56]. Vitamin C is an antioxidant, it inhibits lipid oxidation, it participates in the transmission of GABA receptors and catecholamine biosynthesis. Despite the fact that not all of its functions in the brain are known sufficiently, vitamin C has a therapeutic effect in oxidative stress. Studies among patients with Alzheimer's disease found a significantly lower level of vitamin C in their blood compared with healthy people [57]. Probably higher intake of vitamin C with diet and dietary supplements may delay the decline in cognitive abilities.

## CONCLUSIONS

The potential of modern research techniques allows to provide a lot of evidence for the role of B-vitamins in the pathogenesis of neurological diseases. Due to that, mechanisms of some neurodegenerative diseases were explained and new treatment strategies with vitamins were established. Further research in this field may facilitate new more targeted therapeutic options with the use of vitamins to fight neurodegenerative diseases, which creates new perspectives in medicine.

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