IMPACT OF MEGALOBLASTIC ANEMIA ON THE NERVOUS SYSTEM: PATHOGENESIS AND CLINICAL MANIFESTATIONS

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Abstract. Megaloblastic anemia, primarily caused by vitamin B12 and folate deficiency, is a common hematological disorder associated with significant neurological complications. The nervous system is particularly sensitive to cobalamin deficiency due to its role in myelin synthesis and neuronal metabolism. This review summarizes current data on the pathogenesis of neurological involvement in megaloblastic anemia and highlights the spectrum of clinical manifestations affecting both the central and peripheral nervous systems. Special attention is given to biochemical mechanisms involving homocysteine and methylmalonic acid, which contribute to neurotoxicity and demyelination [1,2]. Early diagnosis and timely treatment are essential to prevent irreversible neurological damage.

Keywords: Megaloblastic anemia; vitamin B12 deficiency; nervous system; neuropathy; homocysteine; methylmalonic acid; neuropsychiatric disorders

Introduction. Megaloblastic anemia is characterized by impaired DNA synthesis, resulting in ineffective hematopoiesis and the formation of large,

immature erythrocytes [2]. The most common causes are deficiencies of vitamin B12 (cobalamin) and folic acid. In addition to hematological abnormalities, megaloblastic anemia has profound effects on the nervous system, often leading to severe neurological and psychiatric disorders [3].

Neurological complications may precede hematological manifestations or occur independently, complicating early diagnosis [4]. These complications significantly affect patients' quality of life and may become irreversible if not treated promptly.

Pathogenesis of neurological damage. Vitamin B12 plays a critical role in two key biochemical reactions: the conversion of homocysteine to methionine and the metabolism of methylmalonyl-CoA to succinyl-CoA [2]. Disruption of these pathways leads to the accumulation of homocysteine and methylmalonic acid, both of which are neurotoxic. Elevated homocysteine levels contribute to neuronal damage by inducing oxidative stress and overstimulation of NMDA receptors, leading to excitotoxicity and vascular endothelial dysfunction [6]. Meanwhile, increased methylmalonic acid interferes with fatty acid synthesis, resulting in abnormal incorporation of fatty acids into neuronal lipids and subsequent myelin degeneration [7].

The destruction of myelin sheaths disrupts nerve conduction, leading to both central and peripheral nervous system dysfunction [3]. Additionally, impaired DNA synthesis affects rapidly dividing cells, further exacerbating neurological damage [6]. Neurological manifestations. Neurological complications of megaloblastic anemia frequently involve the central nervous system.One of the most characteristic conditions is subacute combined degeneration of the spinal cord [1].

Clinically, this condition presents with: sensory ataxia, loss of vibration and position sense, spasticity and weakness. Patients may also develop cognitive

impairment, memory loss, depression, and even psychosis [5]. In severe cases, dementia-like syndromes may occur.

Neuropsychiatric manifestations can occur independently of anemia and may be the first sign of vitamin B12 deficiency [7].

Peripheral nervous system involvement. Peripheral neuropathy is one of the most common neurological manifestations of megaloblastic anemia. It typically presents as symmetric distal sensory neuropathy.

Common symptoms include: paresthesia (tingling and numbness), burning sensations, muscle weakness, gait disturbances.

Clinical studies indicate that distal symmetric neuropathy occurs in a significant proportion of patients with vitamin B12 deficiency [10].

Neuropsychiatric disorders. Megaloblastic anemia is also associated with a wide range of psychiatric manifestations, including depression, anxiety, irritability, hallucinations, and cognitive decline [4]. These symptoms are linked to disrupted methylation processes and neurotransmitter imbalance due to vitamin B12 deficiency [3].

Clinical and laboratory correlations. Neurological symptoms may not always correlate with the severity of anemia. In some cases, patients present with significant neurological deficits despite minimal hematological abnormalities [5].

Laboratory findings typically include: macrocytosis, hypersegmented neutrophils, elevated homocysteine and methylmalonic acid levels. Importantly, normal serum vitamin B12 levels do not always exclude deficiency, making metabolic markers essential for diagnosis [9].

Treatment and prognosis. The cornerstone of treatment is vitamin B12 replacement therapy, administered either orally or intramuscularly [2]. Early

treatment can lead to significant improvement or complete resolution of neurological symptoms. However, prolonged deficiency may result in irreversible neurological damage. Studies show that vitamin B12 supplementation provides clear neurological benefits in symptomatic patients, particularly when initiated early [8,11]. Folic acid supplementation alone may correct hematological abnormalities but does not prevent neurological complications, emphasizing the importance of accurate diagnosis [3].

Discussion. The relationship between megaloblastic anemia and neurological dysfunction is complex and multifactorial. The accumulation of neurotoxic metabolites, impaired myelin synthesis, and disrupted DNA replication all contribute to nervous system damage [6,7]. A key clinical challenge is the variability in presentation, with some patients exhibiting neurological symptoms without anemia [4,12]. This underscores the need for comprehensive evaluation, including biochemical markers.

Conclusion. Megaloblastic anemia has a significant impact on the nervous system, affecting both central and peripheral components. Vitamin B12 deficiency plays a central role in the pathogenesis of neurological damage through multiple biochemical mechanisms [2,3]. Timely diagnosis and appropriate treatment are essential to prevent irreversible complications. Increased awareness of neurological manifestations among clinicians can improve early detection and patient outcomes.

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