UDC 616.832.4-02:[616.391:577.164.1] https://doi.org/10.26641/2307-0404.2024.2.307773

O.D. Shulga [1, 2 *], ***E.A. Popko*** [1], ***A.S. Chabanova*** [1], ***O.G. Kotsiuba*** [1], ***Q. Hussain*** [3]

CLINICAL CASE OF FUNICULAR MYELOSIS IN COMBINATION WITH A CONCOMITANT GENETIC PREDISPOSITION TO FOLATE CYCLE DISORDER

Municipal enterprise "Volyn Regional Clinical Hospital" [1]
Prezudenta Hrushevskoho ave., 21, Lutsk, 43005, Ukraine
Lesya Ukrainka Volyn National University [2]
Voli ave., 13, Lutsk, 43025, Ukraine
"Ukrainian-German Laboratory" [3]
Kravchuka str., 17, Lutsk, 43025, Ukraine
Комунальне підприємство «Волинська обласна клінічна лікарня» [1]
пр. Президента Грушевського, 21, Луцьк, 43005, Україна
Волинський національний університет ім. Лесі Українки [2]
пр. Волі, 13, Луцьк, 43025, Україна
«Українсько-німецька лабораторія» [3]
вул. Кравчука, 17 , Луцьк , 43012, Україна
[*]*e-mail: shulgaolga@ukr.net*

Цитування: Медичні перспективи. 2024. Т. 29, № 2. С. 229-236
Cited: Medicni perspektivi. 2024;29(2):229-236

Key words: *funicular myelosis, B_{12} deficiency anemia, thrombophilia, folate cycle, homocysteine, methylenetetrahydrofolate reductase gene mutation*
Ключові слова: *фунікулярний мієлоз, B_{12}-дефіцитна анемія, тромбофілія, фолатний цикл, гомоцистеїн, мутація гена метилентетрагідрофолатредуктази*

Abstract. Clinical case of funicular myelosis in combination with a concomitant genetic predisposition to folate cycle disorder. Shulga O.D., Popko E.A., Chabanova A.S., Kotsiuba O.G., Hussain Q. *Funicular myelosis (subacute combined degeneration) is a disease characterized by the development of degeneration of the posterior and lateral cords of the spinal cord. Funicular myelosis is a neurological complication of vitamin B_{12} deficiency, which occurs as a result of reduced intake of vitamin B_{12} with food, malabsorption, in connection with taking some drugs (metformin, proton pump inhibitors, and nitrous oxide), with invasion by Diphyllobothrium latum. The disease is usually characterized by the presence of paresthesias, the development of sensitive ataxia, and impaired gait. The aim of the work was to demonstrate a clinical case of funicular myelosis in a young patient in order to improve the diagnostic process, paying attention to the genetic profile and identifying a concomitant predisposition to folate cycle disorder. A clinical case of funicular myelosis in a 39-year-old woman is described. The patient came to the neurology department with complaints of numbness in the upper and lower limbs, periodic shooting pains along the spine when the head is tilted forward. During the neurological examination, the following was observed: a decrease in vibrational, muscle-joint, discrimination sensitivity in the upper limbs, paresthesias in the distal parts of the limbs, and sensitive ataxia. According to the results of the magnetic resonance imaging (MRI) of the spinal cord, a lesion of the posterior cords on the long segment (C2-Th1) was found, which corresponds to the subacute degeneration of the spinal cord, which arose due to the deficiency of holotranscobalamin (active B_{12}). The patient received appropriate treatment and was discharged home. Subsequently, the patient was found to have a concomitant genetic predisposition to folate cycle disorder and the development of thrombophilia. A year later, the woman again came to the neurological department. We carried out a repeated examination, evaluation of the results of the MRI of the cervical spine and other examinations in dynamics. According to the results of the literature analysis, additional markers for the diagnosis of funicular myelosis (in particular, homocysteine), the causes of hyperhomocysteinemia and its effects on the body were described. Timely detection and treatment of vitamin B_{12} deficiency is quite important, since in severe cases the development of spastic paraplegia is possible. Recovery of lost functions depends on the extent of spinal cord damage and the duration of the disease. If anemia is observed together with neurological symptoms, it is necessary to be especially attentive to possible funicular myelosis and to carry out appropriate diagnostic searches. And when detecting hyperhomocysteinemia, it is advisable to take into account other factors that can cause an increase in the level of homocysteine, in addition to a deficiency of vitamins B_6, B_{12} and folic acid.*

Реферат. Клінічний випадок фунікулярного мієлозу в поєднанні із супутньою генетичною схильністю до порушення фолатного циклу. Шульга О.Д., Попко Є.А., Чабанова А.С., Коцюба О.Г., Хуссейн К. *Фунікулярний мієлоз (підгостра комбінована дегенерація) – це захворювання, що характеризується розвитком*

дегенерації задніх та бічних канатиків спинного мозку. Фунікулярний мієлоз є неврологічним ускладненням дефіциту вітаміну B_{12}, який виникає внаслідок зниженого споживання його з їжею, порушення всмоктування, у зв'язку з прийомом деяких ліків (метформін, інгібітори протонної помпи та закис азоту), при інвазії Diphyllobothrium latum. Захворювання зазвичай характеризується наявністю парестезій, розвитком сенситивної атаксії та порушенням ходи. Метою роботи було продемонструвати клінічний випадок фунікулярного мієлозу в молодої пацієнтки для покращення процесу діагностики, приділяючи увагу генетичному профілю та виявленню супутньої схильності до порушення фолатного циклу. Наведено опис клінічного випадку фунікулярного мієлозу у жінки 39 років. Пацієнтка надійшла до неврологічного відділення зі скаргами на затерпання у верхніх і нижніх кінцівках, періодичні прострілюючі болі вздовж хребта при нахилі голови вперед. При неврологічному обстеженні спостерігались: зниження вібраційної, м'язово-суглобової, дискримінаційної чутливості у верхніх кінцівках, парестезії в дистальних відділах кінцівок та сенситивна атаксія. За результатами магнітно-резонансної томографії (МРТ) спинного мозку виявлено ураження задніх канатиків на довгому сегменті (C2-Th1), що відповідає підгострій дегенерації спинного мозку, яка виникла на ґрунті дефіциту голотранскобаламіну (активного B_{12}). Пацієнтка отримала відповідне лікування та була виписана додому. Згодом у пацієнтки було виявлено супутню генетичну схильність до порушення фолатного циклу та розвитку тромбофілії. Через рік жінка знову надійшла до неврологічного відділення. Нами було проведено повторний огляд, оцінка результатів МРТ шийного відділу хребта та інших обстежень в динаміці. Відповідно до результатів аналізу літератури, було описано додаткові маркери для діагностики фунікулярного мієлозу (зокрема, гомоцистеїн), причини гіпергомоцистеїнемії та її вплив на організм. Досить важливим є своєчасне виявлення та лікування дефіциту вітаміну B_{12}, оскільки у тяжких випадках можливий розвиток спастичної параплегії. Відновлення втрачених функцій залежить від об'єму ураження спинного мозку та від тривалості захворювання. Якщо спостерігається анемія разом із неврологічними симптомами, необхідно бути особливо уважними щодо можливого фунікулярного мієлозу і проводити відповідні діагностичні пошуки. А при виявленні гіпергомоцистеїнемії бажано враховувати інші фактори, які можуть спричинити підвищення рівня гомоцистеїну, окрім дефіциту вітамінів B_6, B_{12} і фолієвої кислоти.

Cyanocobalamin, commonly known as Vitamin B_{12}, is sourced from various food products including meat, cheese, liver, and eggs. Consequently, diminished intake, as seen in vegetarian diets, is a primary cause of its deficiency [1]. Upon ingestion, cyanocobalamin is released in the stomach, where it binds with intrinsic factor produced by the gastric parietal cells, forming a complex crucial for absorption in the ileum [2]. Another factor contributing to insufficiency stems from the conditions such as autoimmune gastritis [3], partial or complete gastric resection [4], celiac disease [5], sprue, extensive intestinal resection, and the competitive utilization of vitamin B_{12} by helminths like *Diphyllobothrium latum* [6]. In addition, some medications can lead to vitamin B_{12} deficiency: histamine H_2 receptor antagonists and proton pump inhibitors [7], metformin [8] and nitrous oxide [9].

The timely diagnosis of funicular myelosis is crucial as prompt treatment can prevent irreversible neurological damage. Nonetheless, early detection can be challenging in the absence of hematological signs of vitamin B_{12} deficiency. It is essential to note that severe neurological symptoms can manifest even without anemia, serving as a critical alert for healthcare professionals [10]. Thus, additional assessment of other sensitive and specific biomarkers such as methylmalonic acid or homocysteine levels can be utilized. In particular, the main causes of hyperhomocysteinemia can be a deficiency of folic acid and vitamin B_{12}, as well as genetic factors [10, 11].

The aim of the research was to demonstrate a clinical case of funicular myelosis in a young patient in order to improve the process of diagnosing this disease, paying attention to the genetic profile and identifying a concomitant predisposition to folate cycle disorders.

MATERIALS AND METHODS OF RESEARCH

The research analyzed data sourced from the patient records of the inpatient neurological department in "Volyn Regional Clinical Hospital" of the Volyn Regional Council for the years 2021 and 2022. Approval for this study was obtained from the commission on biomedical ethics in "Volyn Regional Clinical Hospital", VRC (minutes No. 1 dated November 24, 2023). The study adhered to the ethical principles outlined in the Helsinki Declaration "Ethical Principles of Medical Research Involving Humans" and the "General Declaration on Bioethics and Human Rights (UNESCO)". Prior to participation, patients provided informed consent for the application of necessary diagnostic and treatment procedures.

The main and concomitant diseases were diagnosed based on neurological symptoms, incorporating patient history and results from additional tests. These tests encompassed a complete blood count, biochemical blood analysis, genetic testing, helminthic infestation diagnosis, magnetic resonance imaging (MRI) of the spinal cord, and esophagogastroduodenoscopy (EGD). Furthermore, a hematologist was involved in the patient's examination process.

In order to ensure comprehensive and up-to-date information regarding the causes, clinical manifestations, and diagnostic techniques of funicular myelosis, scientific literature analysis was conducted utilizing databases such as PubMed, MedScape, SCOPUS, and Web of Science for the period from 2001 to 2023 using the combination of the terms "subacute combined degeneration", "homocysteine", "vitamin B_{12} deficiency".

RESULTS AND DISCUSSION

A 39-year-old patient S. was admitted to the neurological department of the Volyn Regional Clinical Hospital on September 19, 2022. The patient presented with complaints of numbness in both hands extending to the forearms, as well as numbness in the feet. Additionally, the patient reported experiencing intermittent shooting pains along the spine when tilting the head forward, slight unsteadiness while walking, and periodic episodes of dizziness.

According to the patient, she had been experiencing symptoms for approximately 2 years, initially noticing intermittent numbness in her fingers. She had a history of iron deficiency anemia spanning 5 years and received periodic treatment with iron supplements (Table 1).

Table 1

Dynamics of complete blood count

Indices	Dates of complete blood count			Norm
	13.04.2021	07.06.2021	16.09.2022	
Erythrocytes, 10^{12}/L	3.00	3.36	4.41	3.7-4.7
Hemoglobin, g/L	105	127	134	120-140
Hematocrit, %	29.9	36.2	40.7	36-42
Mean corpuscular volume, μmol3	99.7	108	92.2	81-99
Mean corpuscular hemoglobin, pg	34.9	37.9	30.5	26-32
Mean corpuscular hemoglobin concentration, g/L	35.0	35.2	33.1	32-36
Erythrocyte anisocytosis, %	17.3	15.4	14.4	11.5-15.5
Leukocytes, 10^9/L;	4.39	7.25	6.71	4-9
Platelets, 10^9/L	273	274	261	180-360
Neutrophils, %	50	55	55	47-72
Segmented neutrophils, %	50	55	55	45-72
Lymphocytes, %	40	23	28	19-37
Monocytes, %	7	10	9	3-11
Eosinophils, %	3	12	7	0.5-5
Basophils, %	0	0	1	0-1
ESR, mm/hr	15	10	10	2-15

Patient's condition deteriorated on April 16, 2021, following significant blood loss due to a miscarriage at 20 weeks of pregnancy, resulting in numbness, which extended to the palms and the soles. In May 2021, she sought medical attention in "Volyn Regional Clinical Hospital," presenting complaints of

numbness in both upper and lower extremities, accompanied by shooting pains upon tilting her head forward, which radiated along the spine. On May 18, 2021, a cervical spine MRI (1.5T) was conducted, revealing an MR image indicative of myelopathy along the long segment (C2-Th1) with posterior cord involvement. This finding corresponds to subacute spinal cord degeneration, with potential associations with copper deficiency, vitamin B_{12} and E deficiencies, gastrointestinal tract disorders, while ischemia or compression-related causes are less likely (Fig. 1-2).

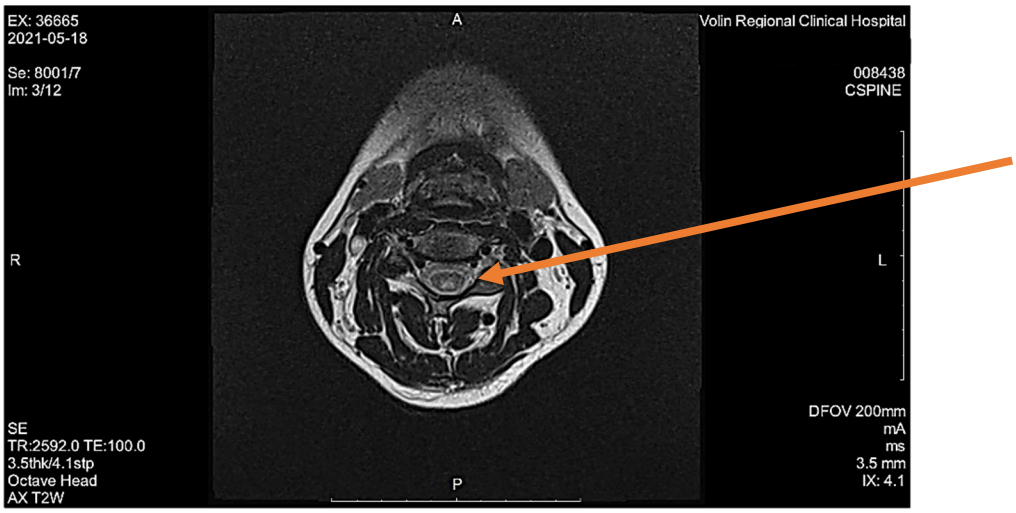

Fig. 1. Magnetic resonance imaging of the cervical spine on May 18, 2021, axial plane, T2 sequence. Hyperintensity in the posterior cords of the spinal cord (arrow)

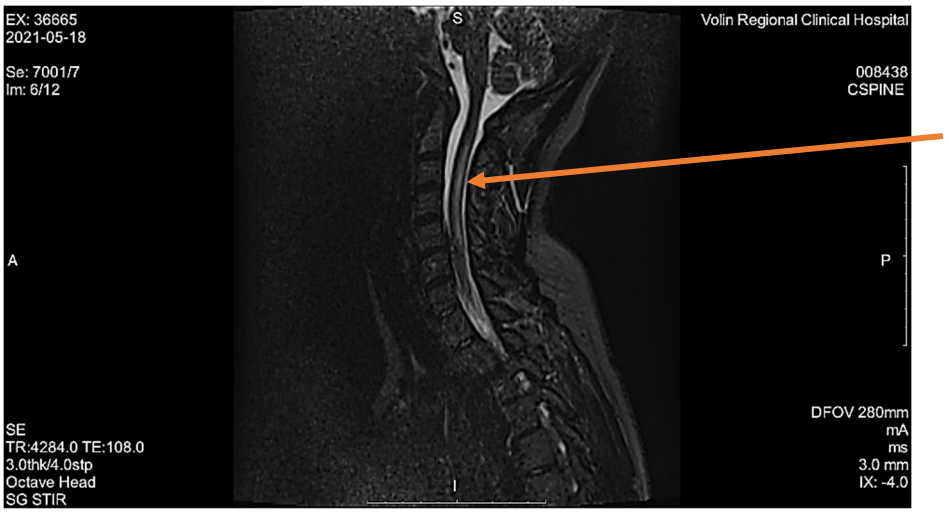

Fig. 2. Magnetic resonance imaging of the cervical spine on May 18, 2021, sagittal plane, STIR sequence. Longitudinal T2 hyperintensity in the posterior cords of the spinal cord at the C2-Th1 level (arrow)

On June 10, 2021, the holotranscobalamin (active B_{12}) level was measured at 6.63 pmol/l (normal range: 25.1-165.0 pmol/l). Considering the examination results along with additional tests, the diagnosis of funicular myelosis was determined. This condition primarily affects the cervical spine at the C2-Th1 level, resulting in significant static and coordination impairments, sensitive ataxia, and compromised deep sensitivity in the upper limbs. The patient also exhibited symptoms consistent with Lhermitte sign. Treatment was initiated with intravenous administration of Cyanocobalamin solution at a dosage of 500 µg per week for one week, followed by a reduced dosage of 400 µg intravenously with an interval of 14 days for two months. Additionally, the patient was prescribed Folic acid tablets, 5 mg once daily, and ferrous iron preparation, 100 mg daily. Subsequently, the patient was discharged from hospital for further

outpatient management. On April 24, 2022, the patient underwent genetic analysis for predisposition to folate cycle disorders, revealing mutations in Methionine synthase reductase (MTRR) and pathological carriage of Methylenetetrahydrofolate reductase (MTHFR), Methionine synthase (MTR) (Table 2). Additionally, polymorphic variants in genes associated with an elevated genetic predisposition to thrombophilia development were identified (Table 3).

Table 2

Folate cycle (24.04.2022)

Gene	Polymorphism	Genotype	Result
MTHFR (*methylenetetrahydrofolate reductase gene*)	**1298A>C**	**A\C**	**Risk allele**
MTR (*methionine synthase gene*)	**2756A>G**	**A\G**	**Risk allele**
MTRR (*methionine synthase reductase gene*)	**66A>G**	**G\G**	**Risk allele**
MTHFR (*methylenetetrahydrofolate reductase gene*)	**677C>T**	**C\T**	**Risk allele**

Note. Polymorphic variants in genes associated with increased genetic susceptibility to folate cycle disorders were identified.

Table 3

Genetic risk of Thrombophilia (24.02.2022)

Gene	Polymorphism	Genotype	Result
FGB (*fibrinogen beta gene*)	**455G>A**	**G/A**	**Risk allele**
TGA2 (*alpha2 integrin gene*)	**807C>T**	**C/T**	**Risk allele**

Note. Polymorphic variants in genes associated with an increased genetic predisposition to thrombophilia development were identified.

On September 19, 2022, the patient was readmitted to the neurological department of Volyn Regional Clinical Hospital for a follow-up examination, aimed at reviewing the results of a cervical spine MRI and other dynamic assessments. Upon admission on September 19, 2022, the patient's neurological status exhibited the following features: tendon reflexes in the hands S>D, present, in the legs S>D, high. Reflex zones appeared to be widened. There was a reduction in vibration, muscle-joint, and discrimination sensitivity in the upper limbs. The patient experienced paresthesias in the distal parts of the limbs and demonstrated uncertain performance in coordination tests. Notably, while assuming the Romberg's pose, significant shakiness, particularly backward, was observed, indicating sensitive ataxia. Additionally, the Marinesco-Radovici sign was positive bilaterally.

The following additional examinations were performed:

09/05/2022 – homocysteine level – 9.01 µmol/L (norm 5-15 µmol/L)

09/16/2022 – general blood test (Table 1), biochemical blood test (Table 4).

Table 4

Biochemical blood test

Index	Date of biochemical blood test	Norm
	16.09.2022	
Holotranscobalamin (active B_{12}), pmol/L	**121.3**	**25.1-165.0 pmol/L**
Iron, µmol/L	**22.4**	**9-30.4 µmol/L**
Ferritin, ng/mL	**48.61**	**12-135 ng/mL**

09/20/2022 – diagnosis of worm infestations – not detected.

09/26/2022 – MRI of the spinal cord: the MR picture corresponds to myelopathy on the long segment (C5-C7) with damage to the posterior cords, which corresponds to subacute degeneration of the spinal cord, it cannot be excluded as a consequence of vitamin B_{12} deficiency (Fig. 3-4).

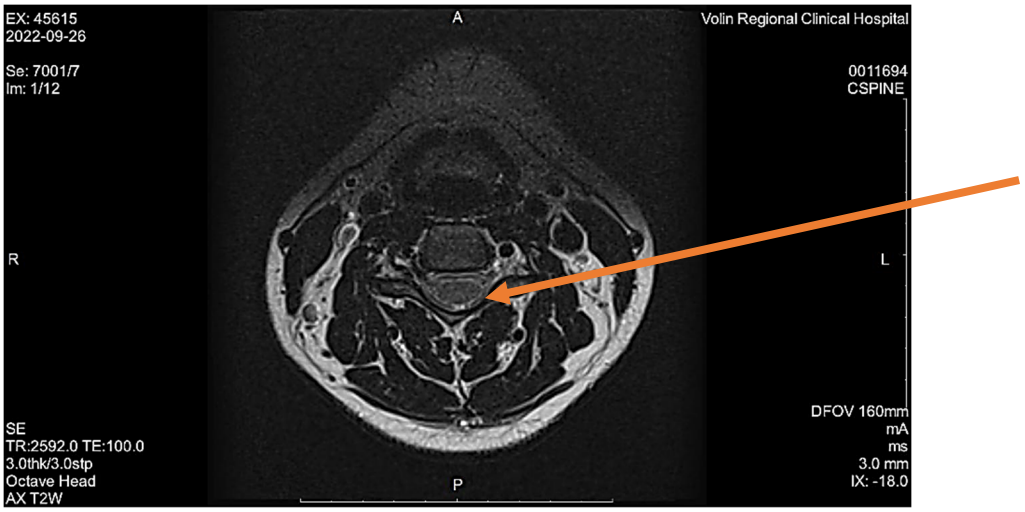

Fig. 3. Magnetic resonance imaging of the cervical spine on September 26, 2022, axial plane, T2 sequence. Hyperintensity in the posterior cords of the spinal cord (arrow)

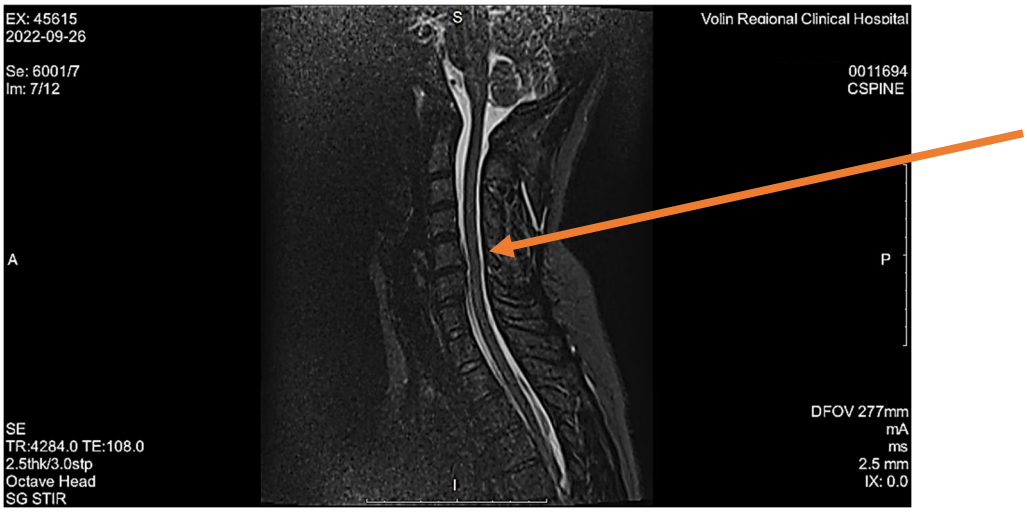

Fig. 4. Magnetic resonance imaging of the cervical spine on September 26, 2022, sagittal plane, STIR sequence. Longitudinal T2 hyperintensity in the posterior cords of the spinal cord at the C5-C7 level (arrow)

09/27/2022 – EGD (esophagogastroduodenoscopy): Atrophic gastritis.

28.09.2022 – Consultation with Hematologist: Diagnosis of congenital thrombophilia confirmed. Disruption of the folate cycle noted, with MTRR mutation detected. Additionally, pathological carriage (manifestation) of MTHFR and MTR observed, displaying a heterozygous manifestation.

The patient received a 500 µg intravenous injection of Cyanocobalamin solution and is continuing to take Folic acid tablets at a dose of 5 mg daily, along with 100 mg of ferrous iron per day. She was discharged showing positive improvement.

Funicular myelosis is a neurological condition marked by the demyelination of the posterior and lateral spinal cord tracts. It is considered a potentially reversible form of myelopathy primarily caused by vitamin B_{12} deficiency.

Cells synthesize two coenzyme forms of vitamin B_{12}: methylcobalamin and 5-deoxyadenosylcobalamin. Methylcobalamin plays a crucial role in DNA synthesis. Inadequate formation of methylcobalamin

leads to ineffective erythropoiesis in the red bone marrow, resulting in anemia. Additionally, there is a decrease in platelets and leukocytes, along with atrophic and inflammatory changes in mucous membranes such as glossitis, esophagitis, and enteritis. On the other hand, 5-deoxyadenosylcobalamin facilitates the conversion of methylmalonic acid to succinate in conversion reactions. In the absence of this coenzyme form, methylmalonic acid accumulates in the body, posing toxicity to nerve cells. This accumulation disrupts myelin formation, leading to the development of funicular myelosis [12].

Funicular myelosis presents in three forms: posterior columnar (primarily affecting the posterior cords), pyramidal (primarily affecting the lateral cords), and combined (involving both lateral and posterior cords simultaneously). Demyelination most commonly occurs in the cervical and thoracic regions of the spinal cord, predominantly affecting the posterior cords in 70-80% of cases and less frequently the pyramidal pathways in 40-50% of cases. Damage to the posterior cords leads to disturbances in proprioceptive and vibrational sensitivity in the lower limbs, resulting in symptoms such as sensory ataxia. Demyelination affecting the lateral cords presents as spastic paraparesis. Alongside sensory and motor impairments, there are also disruptions in pelvic organ function, including urinary retention or urgent urges to urinate. Damage to the posterior roots is characterized by Lhermitte sign–a sensation resembling an electric shock that radiates down the spine or limbs upon bending the neck [10, 13].

Based on our patient's additional examinations in 2022, there was a positive trend compared to 2021: the levels of homocysteine, holotranscobalamin, ferritin, and serum iron are now within normal ranges. Similarly, the lesion of the posterior cords of the spinal cord decreased in volume (segments C5-C7) compared to the initial MRI (C2-Th1). The probable cause of chronic deficiency of vitamin B_{12} was revealed – atrophic gastritis (according to the results of EGD).

The initial diagnosis was straightforward considering the patient's vitamin B_{12} deficiency and macrocytic anemia evident from blood tests, making additional markers as homocysteine unnecessary. Due to a history of miscarriage, the patient underwent genetic testing for thrombophilia and folate cycle disorders, which confirmed a predisposition. Homocysteine is produced during the natural breakdown of methionine, but it can be recycled and reused within the body.

Vitamins B_{12}, B_6, and folic acid, along with the enzyme methylenetetrahydrofolate reductase (MTHFR), play key roles in this process. Inherited mutations in the gene encoding MTHFR, as well as deficiencies in vitamins B_{12}, B_6, and folic acid, can lead to elevated levels of homocysteine in the blood. This condition, known as hyperhomocysteinemia, is linked to an increased risk of cardiovascular and cerebrovascular diseases, venous thrombosis, dementia, and obstetric complications. The exact mechanisms through which homocysteine contributes to these pathologies are not fully understood. It is evident that the level of homocysteine can be reduced through the supplementary use of vitamins B_6, B_{12}, and folic acid, which are also present in our patient's treatment plan.

Recent studies indicate that reducing homocysteine levels with vitamins B_6, B_{12}, and folic acid does not decrease the risk of cardiovascular and venous complications. Consequently, it is hypothesized that homocysteine may serve as a marker of elevated cardiovascular risk rather than being a direct cause [11, 14].

CONCLUSIONS

1. Nervous system damage in B_{12}-deficient anemia signifies a severe and prolonged disease course. Hence, early diagnosis is crucial to prevent irreversible neurological complications.
2. To diagnose funicular myelosis, additionally measuring levels of methylmalonic acid or homocysteine can be used, especially when neurological symptoms are present without anemia or a decrease in vitamin B_{12} levels.
3. When hyperhomocysteinemia is detected, it is important to consider other potential causes of elevated homocysteine in addition to deficiencies in vitamins B_6, B_{12} and folic acid. In our case, the patient has a genetic predisposition to a folate cycle disorder. While research indicates that elevated plasma homocysteine is more of a risk marker than a direct cause of cardiovascular and obstetric complications, understanding genetic predisposition can aid in developing tailored prevention and risk management strategies. Considering the unique genetic background, personalized recommendations and interventions can be more targeted and effective in promoting and maintaining health.

Contributors:

Shulga O.D. – conceptualization, data curation, project administration;

Popko E.A. – resources, writing – review & editing, writing – original draft;

Chabanova A.S. – writing – review & editing, visualization;

Kotsiuba O.G. – writing – review & editing, visualization;

Hussain Q. – writing – original draft.

Funding. This research received no external funding.

Conflict of interests. The authors declare no conflict of interest.

REFERENCES

1. Niklewicz A, Smith AD, Smith A, et al. The importance of vitamin B_{12} for individuals choosing plant-based diets. Eur J Nutr. 2023;62(3):1551-9. doi: https://doi.org/10.1007/s00394-022-03025-4
2. Al-Awami HM, Raja A, Soos MP. Physiology, Gastric Intrinsic Factor. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 14]. PMID: 31536261. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546655/
3. Rustgi SD, Bijlani P, Shah SC. Autoimmune gastritis, with or without pernicious anemia: Epidemiology, risk factors, and clinical management. Therapeutic Advances in Gastroenterology. 2021;14:175628482110387. doi: https://doi.org/10.1177/17562848211038771
4. Gu L, Fu R, Chen P, et al. In Terms of Nutrition, the Most Suitable Method for Bariatric Surgery: Laparoscopic Sleeve Gastrectomy or Roux-en-Y Gastric Bypass? A Systematic Review and Meta-analysis. Obes Surg. 2020;30(5):2003-14.
doi: https://doi.org/10.1007/s11695-020-04488-2
5. Martín-Masot R, Nestares MT, Diaz-Castro J, et al. Multifactorial Etiology of Anemia in Celiac Disease and Effect of Gluten-Free Diet: A Comprehensive Review. Nutrients. 2019;11(11):2557.
doi: https://doi.org/10.3390/nu11112557
6. Sharma K, Wijarnpreecha K, Merrell N. Diphyllobothrium latum Mimicking Subacute Appendicitis. Gastroenterology Res. 2018;11(3):235-7.
doi: https://doi.org/10.14740/gr989w
7. Miller JW. Proton Pump Inhibitors, H2-Receptor Antagonists, Metformin, and Vitamin B-12 Deficiency: Clinical Implications. Adv Nutr. 2018;9(4):511S-518S. doi: https://doi.org/10.1093/advances/nmy023
8. Infante M, Leoni M, Caprio M, Fabbri A. Long-term metformin therapy and vitamin B_{12} deficiency: An association to bear in mind. World J Diabetes. 2021;12(7):916-31.
doi: https://doi.org/10.4239/wjd.v12.i7.916
9. Choi C, Kim T, Park KD, Lim OK, Lee JK. Subacute Combined Degeneration Caused by Nitrous Oxide Intoxication: A Report of Two Cases. Ann Rehabil Med. 2019;43(4):530-4.
doi: https://doi.org/10.5535/arm.2019.43.4.530
10. Means R, Fairfield K. Clinical manifestations and diagnosis of vitamin B_{12} and folate deficiency [Internet]. 2023 [cited 2024 Jan 15]. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-vitamin-b12-and-folate-deficiency?search=subacute%20degeneration%20of%20cord&topicRef=5093&source=see_link#H708835024
11. Rosenson R, Smith C, Bauer K. Overview of homocysteine [Internet]. 2023 [cited 2024 Jan 15]. Available from: https://www.uptodate.com/contents/overview-of-homocysteine?search=hyperhomocysteinemia&topicRef=1120&source=see_link
12. Qudsiya Z, De Jesus O. Subacute Combined Degeneration of the Spinal Cord. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 14]. PMID:32644742. Available from: https://www.ncbi.nlm.nih.gov/books/NBK559316/
13. Bähr M, Frotscher M, Duus P. Duus' topical diagnosis in neurology: Anatomy, physiology, signs, symptoms. Stuttgart: Thieme; 2019.
14. Tinelli C, Di Pino A, Ficulle E, Marcelli S, Feligioni M. Hyperhomocysteinemia as a Risk Factor and Potential Nutraceutical Target for Certain Pathologies. Front Nutr. 2019;6:49.
doi: https://doi.org/10.3389/fnut.2019.00049

Стаття надійшла до редакції 24.11.2023;
затверджена до публікації 18.04.2024