JARMOŁOWICZ, Jakub, BOCZAR, Agata, DRYJA, Patryk, SOLISCH, Sven, STAWICKA, Izabela and ORZOŁEK, Izabela. Minimal hepatic encephalopathy - from cirrhosis to neurological disorders. Journal of Education, Health and Sport. 2024;76:56382. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.76.56382
https://apcz.umk.pl/JEHS/article/view/56382

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 23.11.2024. Revised: 05.12.2024. Accepted: 08.12.2024. Published: 08.12.2024.

Minimal hepatic encephalopathy - from cirrhosis to neurological disorders

Jakub Jarmołowicz[1], Agata Boczar[2], Patryk Dryja[3], Sven Solisch[4],
Izabela Stawicka[5], Izabela Orzołek[6]

1. **Wrocław University Hospital, Borowska 213, 50-556 Wrocław,**

e-mail: kubajarmolowicz98@gmail.com,

ORCID: https://orcid.org/0000-0002-7574-1423

2. **Wrocław University Hospital, Borowska 213, 50-556 Wrocław,**

e-mail: aboczar99@gmail.com,

ORCID: https://orcid.org/0009-0002-3754-598X

3. **Opole University Hospital al. W.Witosa 26 45-401 Opole,**

e-mail: Dryja2@gmail.com

ORCID: https://orcid.org/0009-0009-4276-474X

4. **Opole University Hospital al. W.Witosa 26 45-401 Opole,**

ORCID: https://orcid.org/0009-0002-4769-6095

e-mail: solisch.sven@gmail.com

5. **Central Clinical Hospital, Medical University of Warsaw, Stefana Banacha 1a, 02-097, Warsaw,**

e-mail: izabelastawicka1997@gmail.com,

ORCID: https://orcid.org/0009-0008-3013-1403

6. Czerniakowski Hospital, Stępińska 19/25, 00-739 Warsaw, Poland,

e-mail: iza.orz77@gmail.com

ORCID: https://orcid.org/0000-0003-4723-5504

ABSTRACT

Introduction and aim

Minimal hepatic encephalopathy (MHE) is a subtle but significant brain dysfunction resulting from chronic liver damage, with symptoms that can be difficult to detect. It affects patients' quality of life by causing problems with concentration, memory, and motor coordination. Untreated MHE may progress to more severe neurological disorders, such as overt hepatic encephalopathy. The importance of this condition lies in its impact on patients' daily functioning and the increased risk of accidents, particularly in situations requiring quick responses, such as driving.Neurological symptoms caused by the disease are potentially reversible with treatment.

Materials and Methods

Available literature from the PubMed and Google Scholar databases was reviewed using the following keywords: "minimal hepatic encephalopathy," "hepatic encephalopathy," "cirrhosis," and "SIBO."

Conclusion

The significance of Minimal Hepatic Encephalopathy is crucial from the perspective of preventing further progression and the onset of overt hepatic encephalopathy, as well as improving the quality of life for our patients. Patients and their families are often unaware of the condition, and the cognitive impairments are frequently underestimated. Enhancing diagnostic methods would enable physicians to identify these patients more promptly.

KEYWORDS

“Minimal Hepatic Encephalopathy” ; “hepatic encephalopathy”; ”cirrhosis’’; “SIBO”; “hyperamonemia”

Introduction

Minimal hepatic encephalopathy (MHE) is a subclinical manifestation of hepatic encephalopathy characterized by subtle impairments in cognitive, psychomotor, and attentional functions. This condition occurs in patients with chronic liver diseases, even in the absence of overt neurological symptoms. MHE is associated with a significant reduction in quality of life and an increased risk of progression to overt hepatic encephalopathy. Diagnosis requires the use of advanced psychometric or neurophysiological testing, underscoring the importance of early recognition and therapeutic intervention.[1][2] The spectrum of symptoms is very broad, ranging from subtle manifestations to hepatic coma. [3] MHE is present in approximately 22% to 74% of patients with liver cirrhosis. [4] The quality of life of patients with MHE is impaired.[5][6]

Description of the state of knowledge

The diagnostic and therapeutic approach to Minimal Hepatic Encephalopathy (MHE) is challenging due to the lack of standardized diagnostic criteria and targeted treatments. While certain advancements show promise, such as the use of probiotics for modulating gut microbiota, their long-term efficacy remains under investigation. The most common adverse effects of current therapies for MHE, such as lactulose and rifaximin, include gastrointestinal disturbances like diarrhea and bloating. Despite progress, no causal link between MHE treatments and systemic complications has been definitively established, largely due to the limited availability of high-quality clinical data.

Current classification criteria divide hepatic encephalopathy into two categories

EASL-AASLD z 2014 r.:

1. Covert Hepatic Encephalopathy (CHE):

   This includes minimal hepatic encephalopathy (MHE) and grade 1 hepatic encephalopathy according to the West Haven classification.

2. Overt Hepatic Encephalopathy (OHE):

   A more advanced stage of the condition with clearly observable symptoms.

[7], [8]

Impact on Patients and Recognition Challenges

MHE significantly affects the quality of life. Patients and their families often fail to recognize the condition, attributing symptoms to personality traits or clumsiness. However, it is important to acknowledge the potential negative effects of cognitive and motor dysfunctions on both the patient and their surroundings. These include: 1) Increased risk of daily errors: Such as during vehicle operation or other complex tasks, 2) Higher risk of falls: Due to impaired motor coordination. [9][10]

Aging Population and Diagnostic Challenges

The aging population in Western societies further complicates the diagnosis of MHE, as its symptoms can be easily mistaken for the natural aging process. Cognitive and motor symptoms are subtle, leading to underdiagnosis in older adults. [10]

Prevalence and Societal Costs

Studies indicate that approximately 50% of patients with chronic liver disease may experience neurological impairments associated with MHE. While early detection and diagnosis are vital in advanced societies, they are associated with significant healthcare costs. [11]

Minimal Hepatic Encephalopathy

Minimal hepatic encephalopathy (MHE) has traditionally been described as a subclinical or covert form of hepatic encephalopathy (HE). The primary cause of MHE is the acute or chronic progression of liver cirrhosis. Depending on the severity, it manifests with varying degrees of neuropsychiatric symptoms, ranging from cognitive dysfunction to hepatic coma.

Hepatic encephalopathy (HE)

Hepatic encephalopathy (HE) is a syndrome of cognitive and psychiatric disturbances observed in patients with chronic or acute liver diseases. The liver plays a critical role in detoxifying the body, converting toxic ammonia—produced during protein metabolism—into

urea, which can be safely excreted by the kidneys. When hepatocyte function is impaired, the detoxification processes become insufficient, leading to an increase in blood ammonia levels. Ammonia crosses the blood-brain barrier, exerting toxic effects on the central nervous system and causing the symptoms of encephalopathy.[12][13]

It is estimated that hepatic encephalopathy affects 60–80% of patients with liver cirrhosis. [14]

West Haven Classification

The West Haven Classification is a five-point scale designed to assess the severity of hepatic encephalopathy, facilitating both diagnosis and monitoring of disease progression. From the perspective of diagnosing Minimal Hepatic Encephalopathy, the most relevant grades are 0 and 1. The higher grades of this classification describe more severe stages of hepatic encephalopathy, which do not align with the course of the aforementioned condition.

Degree 0 on this scale describes a state characterized by the absence of clinical abnormalities, although there may be changes observed in neurophysiological and psychomotor tests. This degree is often referred to as Minimal Hepatic Encephalopathy. Currently, there is a lack of standardized tests that allow for rapid and accurate diagnosis, necessitating further expert consultation by physicians. [15]

Degree 1 reflects minor disturbances in concentration, attention, and personality. According to previous terminology, this degree corresponds to Minimal Hepatic Encephalopathy.

Pathophysiology

Liver dysfunction can lead to neurological impairments and a decline in cognitive abilities, resulting from the action of bloodborne factors that affect the permeability or integrity of the blood-brain barrier (BBB). In cases of liver cirrhosis, substances that would normally not cross the BBB penetrate the brain, along with excessive levels of compounds such as ammonia, which typically cross this barrier in limited amounts. The accumulation of these

substances activates pathophysiological mechanisms, leading to adverse effects on the brain.[16]

The triggering factors for the development of MHE include [17]:

1. gastrointestinal bleeding
2. excessive protein
3. hyperkaliemia/hyponatremia (electrolyte imbalance)
4. constipation
5. dehydration

Diagnostic

Initiating the Diagnostic Process for Minimal Hepatic Encephalopathy (MHE):

The diagnostic process for MHE should begin with the recognition during clinical examination of symptoms that may lead the physician to suspect the disease. Key symptoms include fatigue, concentration disturbances, memory impairments, psychiatric problems, and psychomotor slowing.

Physical Examination Findings [15]:

- Liver Cirrhosis: Indications of cirrhosis upon examination.
- Coarse Hand Tremor: Presence of asterixis or flapping tremor.

Further Diagnostic Steps:

The next stage involves detailed assessments that assist clinicians in diagnosing MHE. This includes [1][18][19][20]:

1. Clinical Tests: PHES (Psychometric Hepatic Encephalopathy Score), R-BANS (Repeatable Battery for the Assessment of Neuropsychological Status), ANT (Attention Network Test), CRT (Choice Reaction Time), ICT (Inhibitory Control Test), Stroop App, SCAN (Screen for Cognitive Impairment in Psychiatry).
2. Neurophysiological Examinations: EEG (Electroencephalography), CFF (Critical Flicker Frequency), evoked potential studies.

3. Neuroimaging: CT (Computed Tomography), MRI (Magnetic Resonance Imaging), PET (Positron Emission Tomography).
4. Laboratory Tests: Comprehensive lab evaluations to assess liver function and rule out other conditions.
Diagnostic Recommendations[15]:
Studies indicate the necessity of utilizing 2 to 3 neuropsychomotor tests for accurate diagnosis. If the test results are negative, it is advisable to repeat the assessments after 6 months.

S100B Protein

The 20kDa S100 protein, part of the S100/calmodulin/troponin C-EF hand protein family, plays a role in directing cellular calcium signaling. It was first isolated from glial cells. The detection of S100 protein is possible in various pathological processes, such as malignant melanoma, brain injury, stroke, head trauma, and cardiac arrest.[21][22]
The CanAg100 EIA test is a method for incubating S100 proteins with monomers S100A and S100B. This approach eliminates cross-reactivity with other monomers of this protein, significantly increasing its specificity and effectiveness. Detection of the protein in the test material is interpreted from a streptavidin-coated strip. A positive result is indicated by a blue color, with the intensity of the color correlating proportionally to the protein concentration in the sample.[23]

Numerous scientific studies consistently indicate that the level of S100B protein is elevated in patients with liver cirrhosis and hepatic encephalopathy (HE). [24]

As indicated by the study conducted by Strebel et al., 46% of patients with MHE had elevated levels of this protein. This diagnostic method has the potential to represent the future of faster diagnosis for patients with HE and MHE.[25]

The Role of Gut Microbiota in Minimal Hepatic Encephalopathy

Studies have demonstrated that dysbiosis of the gut microbiota plays a crucial role in the development of Minimal Hepatic Encephalopathy (MHE). Systemic inflammation, hyperammonemia, endotoxins, and neurotoxins are significant factors in the progression of this disease.

Szahab Abid et al. report that treating SIBO in patients with cirrhosis and minimal hepatic encephalopathy (MHE) leads to significant health improvements, both by alleviating SIBO symptoms and enhancing brain function and quality of life in these patients.[26]

Small Intestinal Bacterial Overgrowth (SIBO) is a syndrome characterized by an increase in the bacterial population in the small intestine beyond physiological levels, leading to the manifestation of clinical symptoms. SIBO is a symptom of intestinal dysbiosis. Dysbiosis of the gut microflora leads to increased production of ammonia, enhancing its toxic effect on the nervous system. The cutoff point for recognizing bacterial overgrowth in the small intestine is 10^5 colony-forming units per milliliter (cfu/mL) in an aspirate obtained from the small intestine, which also contains bacteria originating from the colon.[27]

Research indicates that the incidence of Hepatic Encephalopathy (HE) and MHE was significantly higher in patients with SIBO compared to those without intestinal microbiota overgrowth. Inhibition of the activation of the farnesoid X receptor (FXR) and TGR5 receptor due to decreased bile secretion by the liver—resulting from SIBO in patients with liver cirrhosis—impairs the intestinal immune barrier.[28] This condition allows toxins to penetrate the circulatory system. Subsequently, these toxins reach the central nervous system (CNS), where they cause significant damage. SIBO has been confirmed in scientific studies as a factor influencing the development of MHE in patients with liver cirrhosis.[29]

Symptoms of central nervous system damage resulting from the toxic effects of ammonia on nerve cells in the course of HE may include:

1. Consciousness Disorders: Ranging from mild disorientation to coma.
2. Intellectual Function Deterioration: Problems with memory, concentration, and abstract thinking.
3. Personality Changes: Mood swings, irritability, and apathy.
4. Neuromuscular Disorders: Motor slowing and concentration disturbances.

Minimal Hepatic Encephalopathy – Treatment

Randomized controlled trials have demonstrated the positive impact of lactulose and rifaximin on improving the health of patients with Minimal Hepatic Encephalopathy (MHE). The effect of rifaximin was particularly effective in enhancing patients' cognitive and behavioral functions, as could be reliably identified through psychometric testing. It is also worth noting that long-term treatment with a combination of rifaximin and lactulose has shown a beneficial effect in reducing the risk of recurrent hepatic encephalopathy.

However, there is currently a lack of fully randomized protocols for detecting and managing MHE in patients, which leads to discrepancies in the consistency of results across some studies.[17]

Lactulose and rifaximin represent the most effective combination capable of reversing the progression of Minimal Hepatic Encephalopathy in patients with overt liver cirrhosis. Lactulose has proven to be the only effective agent for reversing Minimal Hepatic Encephalopathy, preventing its progression to overt forms, reducing ammonia levels, and improving patients' quality of life, with well-tolerated side effects.[30]

Discussion

From the perspective of physicians across various specialties, such as gastroenterologists, primary care physicians, and other specialists who routinely encounter patients with neurophysiological and neuropsychological symptoms, Minimal Hepatic Encephalopathy (MHE) can present a significant yet often elusive clinical challenge. Individuals with MHE are usually unaware of the subtle disturbances in their cognitive functioning. The absence of obvious central nervous system symptoms that could be detected during routine physical examinations, combined with patients' lack of awareness regarding their declining cognitive abilities, may lead to severe health consequences in the future. However, through effective interdisciplinary collaboration, MHE can be diagnosed, potentially improving patients' quality of life and positively influencing their prognosis. Studies indicate that approximately 50% of patients with MHE develop overt hepatic encephalopathy within a few years.

Minimal Hepatic Encephalopathy represents a milder form of the cognitive and motor impairments associated with the progression of hepatic encephalopathy. The challenge with

this condition lies in its subtle symptoms, which are difficult to detect during a physical examination conducted by a primary care physician. The diagnosis of these impairments relies primarily on the use of specialized diagnostic tests and observation of specific symptoms that may emerge under particular clinical conditions. Although patients with MHE do not exhibit overt clinical symptoms, the condition significantly impacts their daily functioning, gradually reducing their quality of life. Furthermore, these individuals are at an increased risk of developing overt hepatic encephalopathy and generally face poorer health outcomes.

MHE should attract the attention of many physicians who encounter patients with liver dysfunction in their daily practice, but also beyond this group. It turns out that the issue may affect a larger number of undiagnosed patients.

The fundamental importance of Minimal Hepatic Encephalopathy lies in the fact that it occurs in 30–80% of patients with liver cirrhosis, while overt hepatic encephalopathy affects 30–50% of cirrhotic patients.[7][15]

Summary

The presence of MHE is a prognostic factor for the development of overt hepatic encephalopathy; however, it is not always a prerequisite and can sometimes be overlooked during the diagnostic process.[7]

The growing number of patients with neuropsychological disorders poses a challenge for physicians to make accurate diagnoses. Demographic projections for 2050 predict a significant increase in the proportion of seniors, the number of patients exposed to multimorbidity is rising.[31] An aging population is more susceptible to the coexistence of multiple diseases, making complete recovery and maintaining good functioning in elderly patients more difficult. Multimorbidity in older adults increases the risk of various conditions, including dementia and depression. Minimal Hepatic Encephalopathy may also contribute to these disorders, further complicating the diagnostic process. Therefore, physicians should be prepared to recognize MHE to improve patients' quality of life and prevent the progression of the disease.

Liver diseases represent a significant and growing health problem, particularly in developing countries. Complications from these conditions can mimic neurodegenerative symptoms of varying severity, further hindering proper diagnosis and the implementation of appropriate

treatment. Primary care physicians and those working in hospices often encounter patients suffering from neurocognitive disorders. Frequently, elderly patients presenting to physicians have long been diagnosed with dementia as well as other coexisting conditions.

AUTHOR'S CONTRIBUTIONS

The authors confirm contribution to the paper as follows:

Conceptualization: Jakub Jarmołowicz

Methodology: Jakub Jarmołowicz, Izabela Orzołek, Izabela Stawicka and Patryk Dryja

Software: Jakub Jarmołowicz and Agata Boczar

Check: Jakub Jarmołowicz, Sven Solisch and Izabela Stawicka

Formal analysis: Agata Boczar and Patryk Dryja

-Investigation: Agata Boczar and Jakub Jarmołowicz

Resources: Jakub Jarmołowicz

Data curation: Izabela Stawicka, Izabela Orzołek, Jakub Jarmołowicz and Agata Boczar

Writing - rough preparation: Izabela Stawicka, Izabela Orzołek, Jakub Jarmołowicz and Sven Solisch

Writing - review and editing: Jakub Jarmołowicz, Izabela Orzołek, Sven Solisch

Visualization: Patryk Dryja

Supervision: Izabela Orzołek

Project administration: Sven Solisch

All authors have read and agreed with the published version of the manuscript.

FUNDING STATEMENT

This research received no external funding.

ISTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Not applicable.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICTS OF INTERESTS

The author declares no conflict of interest.

REFERENCES

1. Ortiz, María, Carlos Jacas, and Juan Córdoba. "Minimal hepatic encephalopathy: diagnosis, clinical significance and recommendations." Journal of hepatology 42.1 (2005): S45-S53.
2. Stinton, Laura M., and Saumya Jayakumar. "Minimal hepatic encephalopathy." Canadian Journal of Gastroenterology and Hepatology 27.10 (2013): 572-574.
3. Pisarek, Wojciech. "Minimal hepatic encephalopathy – diagnosis and treatment." Gastroenterology Review/Przegląd Gastroenterologiczny, vol. 16, no. 4, 2021, pp. 311-317. doi:10.5114/pg.2021.111389.
4. Dhiman RK, Saraswat VA, Sharma BK, Sarin SK, Chawla YK, Butterworth R i in. Minimalna encefalopatia wątrobowa: oświadczenie konsensusu grupy roboczej Indyjskiego Krajowego Stowarzyszenia Badań nad Wątrobą. J Gastroenterol Hepatol. 2010;25:1029–1041. doi: 10.1111/j.1440-1746.2010.06318.x.
5. Schomerus, H., & Hamster, W. (2001). Quality of life in cirrhotics with minimal hepatic encephalopathy. Metabolic brain disease, 16, 37-41.
6. Ridola, L., Nardelli, S., Gioia, S., & Riggio, O. (2018). Quality of life in patients with minimal hepatic encephalopathy. World journal of gastroenterology, 24(48), 5446.

7. Gairing, Simon Johannes, et al. "Minimal hepatic encephalopathy is associated with a higher risk of overt hepatic encephalopathy and poorer survival." Journal of internal medicine 295.3 (2024): 331-345.
8. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu. and European Association for the Study of the Liver. "EASL Clinical Practice Guidelines on the management of hepatic encephalopathy." Journal of hepatology vol. 77,3 (2022): 807-824. doi:10.1016/j.jhep.2022.06.001
9. Labenz C , Baron JS , Toenges G , Schattenberg JM , Nagel M , Sprinzl MF , i in. Prospektywna ocena wpływu ukrytej encefalopatii wątrobowej na jakość życia i sen u pacjentów z marskością wątroby . Aliment Pharmacol Ther. 2018 ; 48 : 313 – 321 .
10. Kazimierska, Iwona. "Zaburzenia psychiczne i neurologiczne u pacjentów z marskością wątroby." Kurier Medyczny 2021.5: 24-25.
11. Vilstrup, Hendrik, et al. "Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver." Hepatology 60.2 (2014): 715-735.
12. Ridola, L., Faccioli, J., Nardelli, S., Gioia, S., & Riggio, O. (2020). Hepatic encephalopathy: diagnosis and management. Journal of Translational Internal Medicine, 8(4), 210-219.
13. Häussinger, D., Dhiman, R. K., Felipo, V., Görg, B., Jalan, R., Kircheis, G., ... & Vilstrup, H. (2022). Hepatic encephalopathy. Nature Reviews Disease Primers, 8(1), 43.
14. Grata-Borkowska, U., Susło, R., Hańczyc, P., Michalska, M., Lewera, D., & Drobnik, J. (2016). Zaburzenia psychiczne i neurologiczne u pacjentów z encefalopatią wątrobową. Psychiatria, 13(4), 203-209.
15. Bogdanowska-Charkiewicz, Dagmara, et al. "Minimal hepatic encephalopathy–underestimated complication of chronic liver disease." Neuropsychiatria i Neuropsychologia/Neuropsychiatry and Neuropsychology 16.1 (2021): 32-40.
16. Rose, Christopher F., et al. "Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy." Journal of hepatology 73.6 (2020): 1526-1547.
17. Zhan T, Stremmel W. The diagnosis and treatment of minimal hepatic encephalopathy. Dtsch Arztebl Int. 2012 Mar;109(10):180-7. doi: 10.3238/arztebl.2012.0180. Epub 2012 Mar 9. PMID: 22470407; PMCID: PMC3317375.
18. Perspective from Magnetic Resonance Imaging." Journal of Magnetic Resonance Imaging (2023).
19. Hansen, Mads Kingo Guldberg, et al. "Psychometric methods for diagnosing and monitoring minimal hepatic encephalopathy—current validation level and practical use." Metabolic Brain Disease 37.3 (2022): 589-605.
20. Wunsch, Ewa et al. "Normalization of the psychometric hepatic encephalopathy score in Polish population. A prospective, quantified electroencephalography study." Liver

international : official journal of the International Association for the Study of the Liver vol. 33,9 (2013): 1332-40. doi:10.1111/liv.12194

21. Singh, Parul, and Syed Azmal Ali. "Multifunctional role of S100 protein family in the immune system: an update." Cells 11.15 (2022): 2274.
22. Michetti, Fabrizio, et al. "The S100B protein: A multifaceted pathogenic factor more than a biomarker." International Journal of Molecular Sciences 24.11 (2023): 9605.
23. Nelson, Heather A., et al. "Mitigation of biotin interference in manual and automated immunoassays by preconjugating biotinylated antibodies to the streptavidin surface as an alternative to biotin depletion." The Journal of Applied Laboratory Medicine 7.3 (2022): 762-775.
24. Pisarek, Wojciech. "S100 Beta Protein as a Marker of Hepatic Encephalopathy: A Breakthrough in Diagnostics or a False Trail? Review of the Literature." Postępy Higieny i Medycyny Doświadczalnej 76.1 (2022): 128-131.
25. Strebel H, Haller B, Sohn M, Schepp W, Gundling F. Role of brain biomarkers S-100-beta and neuron-specific enolase for detection and follow-up of hepatic encephalopathy in cirrhosis before, during and after treatment with L-ornithine-L-aspartate. GE - Port J Gastroenterol. 2020; 27: 391-403.
26. Abid, Shahab, et al. "Minimal Hepatic Encephalopathy: Effect of H. pylori infection and small intestinal bacterial overgrowth treatment on clinical outcomes." Scientific reports 10.1 (2020): 10079.
27. Sroka, Natalia, et al. "Show Me What You Have Inside—The Complex Interplay between SIBO and Multiple Medical Conditions—A Systematic Review." Nutrients 15.1 (2022): 90.
28. Donaldson GP, Ladinsky MS, Yu KB, Sanders JG, Yoo BB, Chou WC, Conner ME, Earl AM, Knight R, Bjorkman PJ, Mazmanian SK. Mikrobiota jelitowa wykorzystuje immunoglobulinę A do kolonizacji błony śluzowej. Science. 2018;360:795–800. doi: 10.1126/science.aaq0926.
29. Qin N, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Zmiany mikrobiomu jelit ludzkich w marskości wątroby. Nature. 2014;513:59–64. doi: 10.1038/nature13568.
30. Dhiman, Radha K., et al. "Comparative efficacy of treatment options for minimal hepatic encephalopathy: a systematic review and network meta-analysis." Clinical gastroenterology and hepatology 18.4 (2020): 800-812.
31. Adamczyk, M. D. (2018). Specyfika procesów starzenia się społeczeństwa polskiego w kontekście wskaźników zrównoważonego rozwoju. *Wybrane problemy społeczne. Teraźniejszość–Przyszłość*, 112-122.