World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2024 November 21; 30(43): 4672-4676

DOI: 10.3748/wjg.v30.i43.4672

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LETTER TO THE EDITOR

Portocaval shunts' role in gut microbiota and hepatic encephalopathy: The gut-to-brain pathway

Aysun Yakut

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Yuan T

Received: August 13, 2024
Revised: September 11, 2024
Accepted: October 9, 2024
Published online: November 21, 2024
Processing time: 78 Days and 11.1 Hours

Aysun Yakut, Department of Gastroenterology, Istanbul Medipol University Sefakoy Health Practice Research Center, İstanbul 38000, Türkiye

Corresponding author: Aysun Yakut, MD, Doctor, Department of Gastroenterology, Istanbul Medipol University Sefakoy Health Practice Research Center, Tevfikbey District Maslak Cesme Street Kucukcekmece/Istanbul, İstanbul 38000, Türkiye. aysun.yakut@istanbul.edu.tr

Abstract

I read the study by Zhao *et al* with great interest. Although the study design was quite complicated, it was successful in raising awareness of science and relevant researchers. Thirty patients with liver cirrhosis and portal hypertension secondary to chronic hepatitis B were included in the study. They were treated for variceal bleeding and underwent trans-jugular intrahepatic portosystemic shunt to prevent the recurrence of variceal bleeding and to reduce portal pressure. The authors evaluated the effects of changes in gut microbiota (GM) on hepatic encephalopathy secondary to portocaval bypass. The GM is greatly affected by local and general factors, including herbal and medical drugs, a person's dietary characteristics (carnivorous, vegan, vegetarian), supplementary foods, drinking water sources, and living in a city center or town. Therefore, I congratulate Zhao *et al* for their concise and comprehensive study on a multifactorial subject.

Key Words: Chronic hepatitis B; Liver cirrhosis; Transjugular intrahepatic portosystemic shunt; Intestinal microbiota; Hepatic encephalopathy

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: The gut microbiota (GM) has evolved with the host and has become an integral part of the human body. The GM is highly dynamic and changes depending on the person's diseases, diet, habits, living area, water sources and many other factors. Changes in GM abundance can affect some basic immunological, metabolic, structural and neurological functions of the human body. Therefore, the GM has important effects on both the physical and mental health of an individual. In this beautiful study by Zhao *et al* examining GM changes after trans-jugular intrahepatic portosystemic shunt, the effect of the dynamic process in GM and its relationship with hepatic encephalopathy are beautifully described.

Citation: Yakut A. Portocaval shunts' role in gut microbiota and hepatic encephalopathy: The gut-to-brain pathway. *World J Gastroenterol* 2024; 30(43): 4672-4676
URL: https://www.wjgnet.com/1007-9327/full/v30/i43/4672.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i43.4672

TO THE EDITOR

Introduction

Chronic hepatitis B (CHB) is a chronic disease that progresses to liver fibrosis and cirrhosis[1]. It is the leading cause of liver cirrhosis in Asian populations. Portal hypertension is the leading cause of mortality and morbidity in patients with liver cirrhosis. Portal hypertension is a condition in which the portal pressure gradient between the portal vein and the inferior vena cava exceeds 5 mmHg. The main factors that cause this pressure increase are fibrosis and regenerating nodules in the sinusoids, which cause an increase in intrahepatic vascular resistance, while the portal pressure gradient is increased by the addition of vasoconstriction resulting from sinusoidal endothelial dysfunction. The body develops collaterals to reduce the increase in portal pressure and balance it with systemic pressure. When the hepatic venous pressure gradient increases to 10 mmHg or more, varices develop in the portal and caval venous systems at the esophagogastric junction[2]. The increase in hepatic venous pressure gradient causes variceal bleeding, vasodilation in splanchnic arterioles, and a decrease in arterial blood flow in the systemic circulation, leading to systemic hypotension[2]. In contrast, renal vasoconstriction develops with the neurohumoral contribution of the renin-angiotensin-aldosterone system, causing water and sodium retention in the body[2]. As a result of this complex pathogenesis, portal hypertension can be the main trigger for the development of serious complications such as variceal bleeding, ascites, hepatic encephalopathy (HE), hepatorenal syndrome, hepato-pulmonary syndrome, porto-pulmonary syndrome, and hepatic hydrothorax, which may develop during decompensation of cirrhosis. Spontaneous or therapeutic portosystemic shunts cause toxins such as intestinal ammonia and bacterial metabolites to pass directly into the caval system without passing through the portal system, leading to HE. In the management of portal hypertension, nonselective beta-blockers are the first-line medical treatment to reduce portal pressure and its complications. A recent meta-analysis reported that in addition to propranolol, carvedilol was effective in preventing decompensation and improving survival in patients with compensated cirrhosis[3]. In select patients with liver cirrhosis who had recurrent variceal bleeding and were unresponsive to endoscopic band ligation therapy and prophylaxis, trans-jugular intrahepatic portosystemic shunt (TIPS) placement can improve control of cirrhosis complications such as variceal bleeding and ascites and also improve survival in selected patients with liver cirrhosis who failed medical therapy to reduce portal pressure[4]. The preventive TIPS (pTIPS) strategy was demonstrated in a meta-analysis conducted at the Baveno VII workshop on 1327 participants with Child-Pugh score B decompensated cirrhosis and variceal bleeding. In this meta-analysis, pTIPS was compared with medications and endoscopy, resulting in improved bleeding and ascites control and increased 1-year survival in both subgroups[5]. A recent meta-analysis of 12 trials comparing TIPS with standard care for the prevention of refractory ascites and recurrent variceal bleeding showed that TIPS reduced the incidence of further decompensation (hazard ratio: 0.44; 95%CI: 0.37–0.54) and improved survival (2-year cumulative survival probability for TIPS = 0.71 *vs* standard care 0.63; P = 0.0001)[6]. In this editorial, Zhao *et al*[7] demonstrated that changes in gut microbiota (GM) in patients with portal hypertension may influence the development of HE. This study analyzed the changes in GM composition before and after TIPS in Chinese patients with liver cirrhosis and portal hypertension secondary to the hepatitis B virus (HBV), showing that patients without HE exhibited higher GM-related synergism than those with HE. The present study highlighted the need for further discussion of our awareness that GM synergy may predict HE risk after TIPS placement.

CHB

Chronic liver disease causes approximately 2 million deaths worldwide each year[8]. The World Health Organization estimates that 3.5% of the world's population carries the CHB virus (HBV), with 68% of these infected individuals in the Western Pacific (115 million) and Sub-Saharan Africa (60 million)[8]. CHB is a chronic disease that can progress to liver fibrosis and compensated and decompensated liver cirrhosis. Although its prevalence has decreased with universal childhood hepatitis B vaccination programs, HBV carriers are still at risk for chronic liver disease[8].

Trans-jugular intrahepatic portocaval shunt

TIPS is recommended to reduce portal pressure and reduce the risk of rebleeding in decompensated cirrhotic patients with acute variceal bleeding that cannot be controlled by medical and endoscopic band ligation or in decompensated cirrhotic patients with successful endoscopic band ligation but with recurrent variceal bleeding at any time during hospitalization[9]. To manage complications like HE, the decision to perform TIPS should be made with a multidisciplinary approach led by a hepatologist in collaboration with interventional radiology, transplant surgery, nephrology, cardiology, chest diseases, and hematology. The importance of this multidisciplinary approach is emphasized by the protocol specified in Advancing Liver Therapeutic Approaches (ALTA). The ALTA protocol has simplified the management of patients with TIPS by simplifying the complex classification of TIPS indications, new procedural techniques, TIPS stent technology, and TIPS indications[10]. The probability of developing HE is very high in patients with spontaneous or therapeutic shunts. HE is a brain dysfunction that occurs in patients with liver cirrhosis due to severe hepatocellular insufficiency or the presence of portal-to-systemic shunts. The presence of spontaneous portal-to-systemic shunts (SPSS)

may also be responsible for the chronic course of HE. Overt HE is seen in 30%-40% of patients with liver cirrhosis during the natural history of their disease[11]. However, it is difficult to estimate the true epidemiology. A total of 46%-70% of cirrhotic patients with refractory HE have SPSSs on radiological imaging. HE prevalence rates are estimated to be much higher in cirrhotic patients with TIPS and spontaneous or surgical shunts[12-14]. Although medical treatments such as lactulose, rifaximin, and L-ornithine L-aspartate are used in to treat HE, they have their own contradictory aspects. The aim is to reverse the evolving change in consciousness and to provide symptom relief rather than to provide curative treatment to the patient. Options for recurrent/persistent HE include fecal transplantation, TIPS revision, and closure of possible splenorenal shunts[10].

GM

GM has a close relationship with the brain and other systemic organs. GM and a series of metabolites affect the brain through various pathways, such as blood circulation, neuronal transmission, or neurohumoral transmission. It is critical to better understand the synergistic pathway within the gut-brain axis (GBA)[15]. In this editorial by Zhao *et al*[7], they analyzed the changes in GM in patients with liver cirrhosis secondary to CHB and recurrent variceal bleeding after TIPS and presented how certain bacterial species may shape the host GBA. They also aimed to estimate the contribution of the GM changes to the development of HE and evaluated the bacterial composition that may affect host immunity and nerve functions between the HE group and the non-HE group after TIPS. No significant difference was observed in GM abundance between the two groups. However, although it is not clear how bacteria, their products, or metabolites trigger HE between the two groups, the exact mechanism of action and signaling pathways could not be determined. However, the changes in GM in patients with TIPS and the pathogenic microorganisms in the HE group were reported. *Haemophilus* and *Eggerthella* abundance increased in the HE group after TIPS placement, while *Anaerostipes*, *Dialister*, *Butyricicoccus*, and *Oscillospira* decreased. *Eggerthella*, *Streptococcus*, and *Bilophila* abundance increased in the non-HE group, while *Roseburia* and *Ruminococcus* decreased. On the other hand, pathogenic *Morganella* bacteria were seen in the HE group but not in the non-HE group. In another animal experiment study, *Staphylococcaceae*, *Enterobacteriaceae*, and *Lactobacillaceae* abundance was present in the large intestine of HE mice, while *Staphylococcaceae*, *Streptococcaceae*, and *Enterobacteriaceae* species had higher abundance in the small intestine. In addition, TNF-α and IL-1β concentrations were higher in the circulation in these mice and were associated with systemic inflammation[16]. In another study, *Enterobacteriaceae*, *Fusobacteriaceae*, and *Veillonellaceae* were detected in cirrhotic patients with HE, while serum IL-2, IL-13, and IL-23 concentrations were higher and positively correlated[17]. These increased proinflammatory cytokines correlated with the severity of HE and were independent of the stage of liver cirrhosis and the amount of ammonia[18]. The blood-brain barrier does not allow the passage of microorganisms, metabolites, and cytokines in the circulation due to its tight junctions, but proinflammatory cytokines such as TNF-α, ILs, and interferon disrupt the expression of endothelial tight junction proteins, destroy cerebrovascular endothelial cells, activate astrocytes for the inflammatory process, and change their expression and transport pathways in the blood-brain barrier. This situation disrupts the integrity of the blood-brain barrier and further increases surface permeability. This proinflammatory signal initiated by systemic inflammation crosses the damaged blood-brain barrier and forms the basis of the neuroinflammatory response that develops in the brain[18]. Considering that innate immunity affects GBA in this way, it is necessary to consider a very complex spectrum.

Li *et al*[19] showed that GM abundance was changed in patients with CHB compared to patients without CHB. This showed that there is an interaction between the liver and intestine, which can affect the brain and other systems. Supported by animal and human studies, GM changes as HBV-associated liver fibrosis begins and progresses. Therefore, evaluating GM changes after TIPS may not be meaningful alone. However, since the cohort was of the same standard in the study design, it was very important to evaluate GM changes in HE after TIPS. This study showed that GM is quite important and can be affected by manipulative procedures. Zhao *et al*[7] reported that bypassing the portal flow in patients with therapeutic shunts is not the only factor that predisposes patients to HE and that GM may also affect HE through its metabolites and proinflammatory cytokines.

Determining whether microbiota is a suitable disease biomarker and comprehending the temporal and causal links between GM and HE development are critical. Translational methods and larger-scale clinical trials are unquestionably required to assess the effectiveness of microbial therapies in patients, such as probiotics and rifaximin therapy. It is established that the portal system raises the risk of developing HE by entering the systemic circulation right after the shunt. However, this is not seen in every shunted patient, while HE is seen in some shunted patients. The importance of GM can be better understood by early analysis and early treatment of GM. Studying the mechanisms underlying a certain immunological or neurological effect that occurs in the presence or absence of a particular bacterial species or in particular pathogenic conditions will need the use of this methodology. In this instance, the study highlights the need for further research to determine whether and how certain bacterial products or metabolites play a role in the development or maintenance of a disease. The aim of future research should be to identify the precise mechanisms behind the GM-induced pro- and anti-inflammatory responses[15]. For that reason, it will become even more crucial to understand the precise functions of specific bacterial compounds and metabolites within the central nervous system and how they enter the system.

CONCLUSION

In the process of human evolution, it has been increasingly understood in various studies that GM is closely related to human health. The exciting study by Zhao *et al*[7] suggests that the presence of pathogenic *Morgenalla* in HE development after TIPS may provide prophylaxis against possible HE development after shunt treatment by eliminating this strain and

replacing commensal pathogens. In addition, HE can be treated by provoking the presence of commensal bacterial strains in GM instead of standard treatment in decompensated cirrhotic patients with *Morgenalla* strains, eliminating or replacing the abundance of pathogenic GM. This approach is an important result of how to develop better effective interventions and personalized treatment strategies.

FOOTNOTES

Author contributions: Yakut A designed the overall concept and outline of the manuscript, wrote and edited the manuscript, and performed the literature review.

Conflict-of-interest statement: The author declares that she has no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country of origin: Türkiye

ORCID number: Aysun Yakut 0000-0001-7792-8438.

Corresponding Author's Membership in Professional Societies: Turkish Society of Gastroenterology.

S-Editor: Lin C
L-Editor: Filipodia
P-Editor: Zheng XM

REFERENCES

1 **Yakut A**, Aladag M. Noninvasive Tests to Assess Liver Stiffness in Patients with Chronic Hepatitis B: APRI, FIB-4, and FIB-5 Scores. *Int J Clin Pract* 2024; **15** [DOI: 10.1155/2024/5540648]
2 **Ginès P**, Krag A, Abraldes JG, Solà E, Fabrellas N, Kamath PS. Liver cirrhosis. *Lancet* 2021; **398**: 1359-1376 [PMID: 34543610 DOI: 10.1016/S0140-6736(21)01374-X]
3 **Mendizabal M**, Cançado GGL, Albillos A. Evolving portal hypertension through Baveno VII recommendations. *Ann Hepatol* 2024; **29**: 101180 [PMID: 37984701 DOI: 10.1016/j.aohep.2023.101180]
4 **García-Pagán JC**, Saffo S, Mandorfer M, Garcia-Tsao G. Where does TIPS fit in the management of patients with cirrhosis? *JHEP Rep* 2020; **2**: 100122 [PMID: 32671331 DOI: 10.1016/j.jhepr.2020.100122]
5 **Nicoară-Farcău O**, Han G, Rudler M, Angrisani D, Monescillo A, Torres F, Casanovas G, Bosch J, Lv Y, Thabut D, Fan D, Hernández-Gea V, García-Pagán JC; Preemptive TIPS Individual Data Metanalysis, International Variceal Bleeding Study and Baveno Cooperation Study groups. Effects of Early Placement of Transjugular Portosystemic Shunts in Patients With High-Risk Acute Variceal Bleeding: a Meta-analysis of Individual Patient Data. *Gastroenterology* 2021; **160**: 193-205.e10 [PMID: 32980344 DOI: 10.1053/j.gastro.2020.09.026]
6 **Larrue H**, D'Amico G, Olivas P, Lv Y, Bucsics T, Rudler M, Sauerbruch T, Hernandez-Gea V, Han G, Reiberger T, Thabut D, Vinel JP, Péron JM, García-Pagán JC, Bureau C. TIPS prevents further decompensation and improves survival in patients with cirrhosis and portal hypertension in an individual patient data meta-analysis. *J Hepatol* 2023; **79**: 692-703 [PMID: 37141993 DOI: 10.1016/j.jhep.2023.04.028]
7 **Zhao HW**, Zhang JL, Liu FQ, Yue ZD, Wang L, Zhang Y, Dong CB, Wang ZC. Alterations in the gut microbiome after transjugular intrahepatic portosystemic shunt in patients with hepatitis B virus-related portal hypertension. *World J Gastroenterol* 2024; **30**: 3668-3679 [PMID: 39193001 DOI: 10.3748/wjg.v30.i31.3668]
8 **Yakut A**, Aladag M. The relationship between the use of nucleos(t)ide analogs and metabolic parameters in patients with chronic hepatitis B. *Eur Rev Med Pharmacol Sci* 2023; **27**: 9315-9323 [PMID: 37843345 DOI: 10.26355/eurrev_202310_33959]
9 **Vilstrup H**, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, Weissenborn K, Wong P. 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* 2014; **60**: 715-735 [PMID: 25042402 DOI: 10.1002/hep.27210]
10 **Boike JR**, Thornburg BG, Asrani SK, Fallon MB, Fortune BE, Izzy MJ, Verna EC, Abraldes JG, Allegretti AS, Bajaj JS, Biggins SW, Darcy MD, Farr MA, Farsad K, Garcia-Tsao G, Hall SA, Jadlowiec CC, Krowka MJ, Laberge J, Lee EW, Mulligan DC, Nadim MK, Northup PG, Salem R, Shatzel JJ, Shaw CJ, Simonetto DA, Susman J, Kolli KP, VanWagner LB; Advancing Liver Therapeutic Approaches (ALTA) Consortium. North American Practice-Based Recommendations for Transjugular Intrahepatic Portosystemic Shunts in Portal Hypertension. *Clin Gastroenterol Hepatol* 2022; **20**: 1636-1662.e36 [PMID: 34274511 DOI: 10.1016/j.cgh.2021.07.018]
11 **Garcia-Tsao G**, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017; **65**: 310-335 [PMID: 27786365 DOI: 10.1002/hep.28906]
12 **Bai M**, Qi X, Yang Z, Yin Z, Nie Y, Yuan S, Wu K, Han G, Fan D. Predictors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients: a systematic review. *J Gastroenterol Hepatol* 2011; **26**: 943-951 [PMID: 21251067 DOI: 10.1111/j.1440-1746.2011.06663.x]
13 **Riggio O**, Efrati C, Catalano C, Pediconi F, Mecarelli O, Accornero N, Nicolao F, Angeloni S, Masini A, Ridola L, Attili AF, Merli M. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. *Hepatology* 2005; **42**: 1158-1165

[PMID: 16250033 DOI: 10.1002/hep.20905]

14 **Simón-Talero M**, Roccarina D, Martínez J, Lampichler K, Baiges A, Low G, Llop E, Praktiknjo M, Maurer MH, Zipprich A, Triolo M, Vangrinsven G, Garcia-Martinez R, Dam A, Majumdar A, Picón C, Toth D, Darnell A, Abraldes JG, Lopez M, Kukuk G, Krag A, Bañares R, Laleman W, La Mura V, Ripoll C, Berzigotti A, Trebicka J, Calleja JL, Tandon P, Hernandez-Gea V, Reiberger T, Albillos A, Tsochatzis EA, Augustin S, Genescà J; Baveno VI-SPSS group from the Baveno Cooperation. Association Between Portosystemic Shunts and Increased Complications and Mortality in Patients With Cirrhosis. *Gastroenterology* 2018; **154**: 1694-1705.e4 [PMID: 29360462 DOI: 10.1053/j.gastro.2018.01.028]

15 **Rutsch A**, Kantsjö JB, Ronchi F. The Gut-Brain Axis: How Microbiota and Host Inflammasome Influence Brain Physiology and Pathology. *Front Immunol* 2020; **11**: 604179 [PMID: 33362788 DOI: 10.3389/fimmu.2020.604179]

16 **Kang DJ**, Betrapally NS, Ghosh SA, Sartor RB, Hylemon PB, Gillevet PM, Sanyal AJ, Heuman DM, Carl D, Zhou H, Liu R, Wang X, Yang J, Jiao C, Herzog J, Lippman HR, Sikaroodi M, Brown RR, Bajaj JS. Gut microbiota drive the development of neuroinflammatory response in cirrhosis in mice. *Hepatology* 2016; **64**: 1232-1248 [PMID: 27339732 DOI: 10.1002/hep.28696]

17 **Bajaj JS**, Ridlon JM, Hylemon PB, Thacker LR, Heuman DM, Smith S, Sikaroodi M, Gillevet PM. Linkage of gut microbiome with cognition in hepatic encephalopathy. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G168-G175 [PMID: 21940902 DOI: 10.1152/ajpgi.00190.2011]

18 **Luo M**, Xin RJ, Hu FR, Yao L, Hu SJ, Bai FH. Role of gut microbiota in the pathogenesis and therapeutics of minimal hepatic encephalopathy *via* the gut-liver-brain axis. *World J Gastroenterol* 2023; **29**: 144-156 [PMID: 36683714 DOI: 10.3748/wjg.v29.i1.144]

19 **Li YG**, Yu ZJ, Li A, Ren ZG. Gut microbiota alteration and modulation in hepatitis B virus-related fibrosis and complications: Molecular mechanisms and therapeutic inventions. *World J Gastroenterol* 2022; **28**: 3555-3572 [PMID: 36161048 DOI: 10.3748/wjg.v28.i28.3555]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2024 Baishideng Publishing Group Inc. All rights reserved.