Increased occurrence of brain abscesses in cirrhotic patients: A population-based 3-year follow-up study

Yen-Chun Chen[1], Tsung-Hsing Hung[1-2], Kuo-Chih Tseng[1-2], Chih-Wei Tseng[1-2], Yu-Hsi Hsieh[1-2], Chih-Chun Tsai[3], Chen-Chi Tsai[1-2]

[1]Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation , Medicine, Chiayi County, Taiwan
[2]Tzu Chi University, School of Medicine, Hualien, Taiwan
[3]Department of Mathematics, Tamkang University, Tamsui, Taiwan

Cite this article as: Chen YC, Hung TH, Tseng KC, et al. Increased occurrence of brain abscesses in cirrhotic patients: a population-based 3-year follow-up study. Turk J Gastroenterol 2017; 28: 342-6.

Original Article

ABSTRACT

Background/Aims: Cirrhotic patients are prone to various infectious diseases. However, it is still unknown if the occurrence of a brain abscess is associated with cirrhosis. The purpose of this study was to identify the relationship between the occurrence of a brain abscess and cirrhosis.

Materials and Methods: The National Health Insurance Database, which is derived from the Taiwan National Health Insurance program, was used to collect data from 40,878 patients with cirrhosis and from 40,896 randomly selected age- and sex-matched patients. All patients were followed up to identify the occurrence of brain abscesses in 3 years.

Results: A total of 143 patients (0.17%) were diagnosed with brain abscesses in the 3-year follow-up period. There were 94 (0.23%) patients with cirrhosis and 49 (0.12%) without cirrhosis (p<0.001). After regression analysis, cirrhotic patients had a higher risk of occurrence of brain abscesses than non-cirrhotic patients (hazard ratio: 1.88, 95% confidence interval: 1.30-2.72; p=0.001). In addition, the risk of occurrence of brain abscesses was higher in complicated cirrhotic patients than in non-complicated cirrhotic patients (adjusted hazard ratio: 2.07, 95% confidence interval: 1.36-3.14; p=0.001).

Conclusion: Cirrhotic patients, particularly those with complicated cirrhosis, have a higher risk of the occurrence of brain abscesses than non-cirrhotic patients.

Keywords: Cirrhosis, brain abscess, complicated cirrhosis

INTRODUCTION

Cirrhotic patients are prone to infections due to impaired innate immunity and a portosystemic shunt (1-4). Most infections, such as spontaneous bacterial peritonitis, pneumonia, urinary tract infections, and septicemia, have been proved to be associated with cirrhosis (1-7). However, other infectious diseases have not been well investigated. It is still unknown if other infections are associated with cirrhosis.

A brain abscess is a rare infectious condition in the general population. It has been proved to be associated with many underlying diseases, such as alcoholism, diabetes mellitus (DM), chronic renal failure (CRF), and malignancy (8-13). A brain abscess sometimes occurs in cirrhotic patients (8-18). Theoretically, cirrhotic patients should have a higher risk of the occurrence of brain abscesses than the general population due to their impaired immunity (19). However, the relationship between cirrhosis and the occurrence of a brain abscess has not yet been established due to the lack of a large population. We used National Health Insurance Research Database (NHIRD) to enroll a large population of cirrhotic and non-cirrhotic patients who were followed up to determine the occurrence of brain abscesses in 3 years. The purpose of this study was to

Address for Correspondence: Chen-Chi Tsai E-mail: antibody_1@msn.com
Received: October 22, 2013 **Accepted:** January 25, 2014 **Available Online Date:** August 9, 2017

determine whether cirrhosis is a predisposing factor for the occurrence of a brain abscess.

MATERIALS AND METHODS

Database

The database used was from the NHIRD in Taiwan; it was established and is maintained by the Taiwan National Health Insurance Bureau and the National Health Research Institute. The database was used to identify all discharged patients in Taiwan. The Taiwan National Health Insurance Program was established in 1995 and included all citizens residing in Taiwan. The National Health Insurance Bureau covers >99% of Taiwan's population.

All researchers who use the NHIRD need to have their study protocols evaluated by the National Health Research Institute and protect the privacy of health care providers and patients. This study was approved by the National Health Research Institute (application and agreement number 100101).

Compliance with Ethical Requirements

This study was initiated after approval from the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital Taiwan (IRB B1010410). As all identifying personal information was removed from the secondary files before analysis, the review board waived requirement for written informed consent from the patients involved.

Patient Population

This retrospective study included patients discharged with a diagnosis of cirrhosis (ICD-9-CM codes 571.5 or 571.2 in the database) between January 1, 2004 and December 31, 2004. When cirrhotic patients had refractory ascites, episodes of esophageal/gastric variceal bleeding, or hepatic encephalopathy, there were considered as having complicated cirrhosis. Patients <30 years old were not included to exclude congenital anomaly-related cirrhosis. Because of the different mechanism of cirrhosis, biliary cirrhotic patients (ICD-9-CM code 571.6) were not included.

A total of 40,878 cirrhotic patients without baseline brain abscesses were enrolled. The reference group was composed of 40,896 randomly selected sex- and age-matched patients. Each patient (n=81,774) was followed up for a 3-year period starting from their first hospitalization to the diagnosis of brain abscesses (ICD-9-CM code 324).

Statistical Analysis

In this 3-year follow-up, Cox proportional hazard regression was performed to evaluate the association between the occurrence of a brain abscess and cirrhosis. Comorbid diseases were considered if the condition was noted at the first hospitalization. Comorbid medical disorders included alcoholism (ICD-9-CM codes 291, 303, 305.00-305.03, and 571.0-571.3), DM (ICD-9-CM code 250), gouty arthritis (ICD-9-CM code 274), CRF (ICD-9-CM code 585), solid organ transplantation (SOT) (ICD-9-CM codes V42.0, V42.1, V42.7), rheumatoid arthritis (RA) (ICD-9-CM code 714), and connective tissue disease (CTD) (ICD-9-CM code 710). Age was defined as a continuous covariate in the Cox proportional hazard regression model. The influence of the covariates was evaluated using Cox regression. Hazard ratios (HRs) and 95% confidence intervals (CIs) using a significance level of 0.05 were calculated. Statistical Package for Social Sciences version 13.0 (SPSS Inc.; Chicago, IL, USA) was used to perform the analyses.

Table 1. Demographic characteristics and comorbid disorders in 40,878 cirrhotic patients and 40,896 non-cirrhotic patients

	Cirrhotic Patients		Non-cirrhotic Patients		
	Number	%	Number	%	p
Gender					0.983
Male	29,071	71.1	29,081	71.1	
Female	11,807	28.9	11,815	28.9	
Age, years					0.620
30-44	7,091	17.3	7,100	17.7	
45-59	13,093	32.0	13,105	32.0	
60-74	14,178	34.7	14,176	34.7	
>75	6,516	15.9	6,515	15.9	
Gout	803	2.0	1088	2.7	<0.001
DM	8,034	19.7	7,189	17.6	<0.001
CRF	1,251	3.1	1,151	2.8	0.038
CTD	60	0.1	77	0.2	0.171
Alcoholism	7,967	19.5	684	1.7	<0.001
RA	51	0.1	120	0.3	<0.001
SOT	129	0.3	77	0.2	<0.001

CTD: connective tissue disease; SOT: solid organ transplantation; DM: diabetes mellitus; CRF: chronic renal failure; RA: rheumatoid arthritis

RESULTS

Table 1 shows the distribution of demographic characteristics and comorbid medical disorders between cirrhotic and non-cirrhotic patients. Among the 81,774 included patients, there were 143 (0.17%) patients with brain abscesses during the 3-year follow-up period. Of these, 94 (0.23%) were in the cirrhosis group, whereas only 49 (0.12%) were in the reference group (non-cirrhotic patients) (p<0.001).

The results of Cox regression analysis are provided in Table 2. After adjusting for patients' gender, age, and comorbid disorders, the HR of cirrhotic patients for the occurrence of

Table 2. Adjusted hazard ratios for the occurrence of brain abscesses during the 3-year follow-up period following the first hospitalization

Variable	Hazard Ratio	95% Confidence Interval	p
Cirrhosis	1.88	1.30-2.72	0.001
CTD	6.77	1.49-30.84	0.013
SOT	4.55	1.12-18.59	0.034
Age	0.98	0.96-0.99	0.001
Male	1.03	0.68-1.56	0.905
DM	1.40	0.94-2.08	0.102
Alcoholism	1.47	0.93-2.30	0.097
CRF	1.95	0.90-4.20	0.089
RA	6.09	1.35-27.45	0.019
Gout	2.67	1.35-5.28	0.005

CTD: connective tissue disease; SOT: solid organ transplantation; DM: diabetes mellitus; CRF: chronic renal failure; RA: rheumatoid arthritis

Table 3. Crude and adjusted hazard ratios for the occurrence of brain abscesses among 8,754 complicated cirrhotic patients and 32,124 non-complicated cirrhotic patients

Brain Abscess	Non-complicated Cirrhosis	Complicated Cirrhosis	p
Yes, n (%)	57 (0.18)	37 (0.42)	
No, n (%)	32,067 (99.8)	8,717 (99.6)	
Crude HR (95% CI)	1	2.39 (1.58-3.61)	<0.001
*Adjusted HR (95% CI)	1	2.07 (1.36-3.14)	0.001

CI: confidence interval; HR: hazard ratio
*Adjustments were made for patient's gender, age, gout, diabetes mellitus, chronic renal failure, connective tissue disease, solid organ transplantation, rheumatoid arthritis, and alcoholism.

brain abscesses during the 3-year follow-up period was 1.88 (95% CI: 1.30-2.72, p=0.001). After regression, other significant predisposing factors for brain abscesses included CTD (HR: 6.77, 95% CI: 1.49-30.94; p=0.013), SOT (HR: 4.55, 95% CI: 1.12-18.59; p=0.034), RA (HR: 6.09, 95% CI: 1.35-27.45; p=0.019), and gouty arthritis (HR: 2.67, 95% CI: 1.35-5.28; p=0.005).

Of the 40,878 cirrhotic patients, there were 8,754 (21.4%) with complicated cirrhosis. Table 3 summarizes the crude and adjusted HRs of complicated cirrhotic patient for the occurrence of brain abscesses. Complicated cirrhotic patients had higher crude HRs for the occurrence of brain abscesses than non-complicated cirrhotic patients during the 3-year follow-up period. After Cox hazard regression that adjusted for gender, age, and comorbid disorders, complicated cirrhotic patients were more likely to have brain abscesses during the 3-year follow-up period (HR: 2.07, 95% CI: 1.36-3.14; p=0.001) than non-complicated cirrhotic patients.

DISCUSSION

A brain abscess is a focal encapsulated infection within the brain parenchyma. It is a life-threatening condition, and its mortality rate is approximately 7.1%-25% (5-7). The current study showed that cirrhotic patients were more prone to brain abscesses than non-cirrhotic patients. Hematogenic spreading is the most important route for brain abscesses (8-13). Cirrhosis was proved to increase the risk of bacterial bloodstream infection due to reticuloendothelial dysfunction, decreased opsonic activity of the ascitic fluid, neutrophil leukocyte dysfunction, and a portosystemic shunt (1-7). In addition, alcohol abuse and malnutrition are contributing factors to the immunocompromised state in some cirrhotic patients. This may be the reason why cirrhotic patients have brain abscess more frequently than non-cirrhotic patients.

In the current study, we found that the incidence of brain abscesses was higher in complicated cirrhotic patients than in non-complicated cirrhotic patients. This shows that the severity of cirrhosis is positively correlated with the risk of the occurrence of a brain abscess. Cirrhotic patients, particularly complicated cirrhotic patients, require endoscopic treatments, which can cause procedure-related mucosal damage and microbial flora translocation into the bloodstream (20). Some cirrhotic patients had brain abscesses immediately after they underwent endoscopic therapy (16-18). Prophylactic antibiotics have been recommended by The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy in several patients including cirrhotic patients with acute gastrointestinal bleeding (20). However, it is still unknown whether prophylactic antibiotics can prevent the occurrence of brain abscesses in cirrhotic patients undergoing endoscopic therapies. This requires further studies to provide more evidence.

In Taiwan, hepatitis B or C virus infection is the most important cause of cirrhosis (21,22). Our study revealed that the causes of cirrhosis were alcoholism (19.5%) and viral infections (80.5%). In clinical practice, steroids or other immunosuppressive agents are avoided in cirrhotic patients due to the fear of viral hepatitis fare-up. However, multiple immunosuppressive agents are always used in SOT, RA, gouty arthritis, and CTD patients. We selected these conditions as confounding factors to regress our results. Therefore, the impact of immunosuppressive agents in the occurrence of brain abscesses can be diminished.

The common clinical signs and symptoms of brain abscesses are as follows: headache, mental status change, seizure, and focal neurological signs (8-11). However, these symptoms may be confused with hepatic encephalopathy in cirrhotic patients. In addition, cirrhotic patients with bacterial infection often do not have fever (5-7). Therefore, a brain abscess is likely to be neglected in cirrhotic patients with

Original Article

hepatic encephalopathy. The actual incidence of a brain abscess in cirrhotic patients may have been underestimated in the present study.

This study has several limitations. First, the database had incomplete information. For example, we could not obtain the details of microorganisms isolated from brain abscesses. Whether cirrhotic patients with brain abscesses have a tendency to be infected with some kinds of microorganisms has not been identified. Second, the true frequency of the occurrence of a brain abscess may be underestimated in the present study. The symptoms for a brain abscess may be easily confused in cirrhotic patients with hepatic encephalopathy. Third, patients whose records were in the database were mainly from Taiwan. Hence, we do not know if ethnic difference plays a role in the occurrence of brain abscesses in cirrhotic patients. Fourth, we could not obtain information on therapy from the database. Cirrhotic patients, with or without hepatoma, may receive a specific treatment such as esophageal variceal ligation or transarterial chemoembolization. Whether specific treatments are associated with the occurrence of a brain abscess also requires further clarification. Fifth, we could not distinguish the severity of liver cirrhosis using the Child-Pugh scores in our study.

In spite of the limitations, our study is currently the most complete nationwide population-based study for identifying the relationship between cirrhosis and the occurrence of a brain abscess. It demonstrated that cirrhotic patients have a higher risk of the occurrence of brain abscesses than non-cirrhotic patients. Furthermore, complicated cirrhotic patients have a higher risk of the occurrence of brain abscesses than non-complicated cirrhotic patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of the Buddhist Dalin Tzu Chi Hospital Taiwan (IRB B1010410).

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Y.C.C., T.H.H., C.C.T.; Design - T.H.H., C.C.T.; Supervision - K.C.T., C.W.T., Y.H.H.; Resource - T.H.H., C.C.T.; Materials - T.H.H., C.C.T.; Data Collection and/or Processing - T.H.H., C.C.T.; Analysis and/or Interpretation - T.H.H., C.C.T.; Literature Search - Y.C.C., T.H.H., C.C.T.; Writing - Y.C.C., T.H.H., C.C.T.; Critical Reviews - K.C.T., C.W.T., Y.H.H.

Acknowledgements: This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes (Registered number: 100101). The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health or National Health Research Institutes.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Christou L, Pappas G, Falagas ME. Bacterial infection-related morbidity and mortality in cirrhosis. Am J Gastroenterol 2007; 102: 1510-7. [CrossRef]
2. Menon KV, Kamath PS. Managing the complications of cirrhosis. Mayo Clin Proc 2000; 75: 501-9. [CrossRef]
3. Resnick RH. Portal hypertension and its complications-an overview. J Clin Gastroenterol 1980; 2: 259-67. [CrossRef]
4. Benvegnù L, Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. Gut 2004; 53: 744-9. [CrossRef]
5. Navasa M, Fernández J, Rodés J. Bacterial infections in liver cirrhosis. Ital J Gastroenterol Hepatol 1999; 31: 616-25.
6. Toledo C, Flores C, Sáenz M, et al. Bacterial infections in hepatic cirrhosis. Rev Med Chil 1994; 122: 788-94.
7. Navasa M, Rodés J. Bacterial infections in cirrhosis. Liver Int 2004; 24: 277-80. [CrossRef]
8. Xiao F, Tseng MY, Teng LJ, Tseng HM, Tsai JC. Brain abscess: clinical experience and analysis of prognostic factors. Surg Neurol 2005; 63: 442-9. [CrossRef]
9. Kao PT, Tseng HK, Liu CP, Su SC, Lee CM. Brain abscess: clinical analysis of 53 cases. J Microbiol Immunol Infect 2003; 36: 129-36.
10. Nathoo N, Nadvi SS, Narotam PK, van Dellen JR. Brain abscess: management and outcome analysis of a computed tomography experience with 973 patients. World Neurosurg 2011; 75: 716-26. [CrossRef]
11. Ni YH, Yeh KM, Peng MY, Chou YY, Chang FY. Community-acquired brain abscess in Taiwan: etiology and probable source of infection. J Microbiol Immunol Infect 2004; 37: 231-5.
12. Grigoriadis E, Gold WL. Pyogenic Brain Abscess Caused by Streptococcus pneumoniae: Case Report and Review. Clin Infect Dis 1997; 25: 1108-12. [CrossRef]
13. Carpenter J, Stapleton S, Holliman R. Retrospective analysis of 49 cases of brain abscess and review of the literature. Eur J Clin Microbiol Infect Dis 2007; 26: 1-11. [CrossRef]
14. Chung CL, Lieu AS, Chen IY, Kwan AL, Howng SL. Brain abscess in adult cirrhotic patients: two case reports. Kaohsiung J Med Sci 2007; 23: 34-9. [CrossRef]
15. Kato J, Koda M, Fujise Y, et al. Brain abscess in a patient with decompensated cirrhosis. J Med Cases 2011; 2: 55-7. [CrossRef]
16. Cohen FL, Koerner RS, Taub SJ. Solitary brain abscess following endoscopic injection sclerosis of esophageal varices. Gastrointest Endosc 1985; 31: 331-3. [CrossRef]
17. Shih HI, Lee HC, Chuang CH, Ko WC. Fatal Klebsiella pneumoniae meningitis and emphysematous brain abscess after endoscopic variceal ligation in a patient with liver cirrhosis and diabetes mellitus. J Formos Med Assoc 2006; 105: 857-60. [CrossRef]
18. Laviv Y, Ben-Daviv U, Vated M, Rapparort ZH. Brain abscess following endoscopic ligation of esophageal varicose veins. Acta Neurochir 2010; 152: 733-4. [CrossRef]
19. Ashare A, Morick MM, Powers LS, Yarovinsky T, Hunninghake GW. Severe bacteremia results in a loss of hepatic bacterial clearance. Am J Respir Crit Care Med 2006; 173: 644-52. [CrossRef]

20. Banerjee S, Shen B, Baron TH, et al. Antibiotic prophylaxis for gastrointestinal endoscopy. Gastrointest Endosc 2008; 67: 791-8. [CrossRef]
21. Hsu HC, Lin WS, Tsai MJ. Hepatitis-B surface antigen and hepatocellular carcinoma in Taiwan. With special reference to types and localization of HBsAg in the tumor cells. Cancer 1983; 52: 1825-32. [CrossRef]
22. Tsai JF, Chang WY, Jeng JE, et al. Hepatitis C virus infection as a risk factor for non-alcoholic liver cirrhosis in Taiwan. J Med Virol 1993; 41: 296-300.[CrossRef]