RESEARCH LETTER

Thyroxine Levels Predict the Development of Brain Failure in Patients With Cirrhosis in Indian Population

Hepatic encephalopathy (HE) is a reversible common decompensating neuropsychiatric disorder occurring in up to 45% of patients with cirrhosis during their lifetime.[1] In-hospital development of grade 3–4 overt HE (brain failure) is not uncommon and significantly impacts the healthcare burden. Therefore, it is important to identify patients at risk of developing brain failure to prevent morbidity and mortality.[2] Until recently, there were no simple biomarkers reported to predict the development of brain failure. A multicenter study including 602 patients from North America (United States and Canada) reported that four metabolites at the time of admission could aid in predicting brain failure.[3] These four metabolites included low thyroxine (T4) and maltose and high methyl 4-hydroxybenzoate sulfate, and 3–4 dihydroxy butyrate. The study was prospectively validated in 81 patients in the United States. A similar small study, including 15 patients from Turkey, also reported low T4 levels in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) and HE.[4] Although thyroxine level assessment is easy and universally available, external validation is still lacking, which we aimed to evaluate in our center.

In this single-center prospective cohort study, we enrolled consecutive willing adult patients with cirrhosis admitted to AIG Hospital, Hyderabad, from September 10, 2022, to March 1, 2023. Patients with brain failure at admission, patients with an unclear cirrhosis diagnosis, hepatocellular carcinoma, acute-on-chronic liver failure, liver transplant recipients, and those unwilling were excluded. The primary objective was to assess the incidence of brain failure, and the secondary was to compare the characteristics of patients who developed brain failure, including baseline demographics, duration of hospital stay, and in-hospital mortality with those who did not develop brain failure. The study was approved by the Institutional Ethics Committee (IEC) bearing the IEC number AIG/IEC-BH&R 34/08.2022-02 and was performed in accordance with the Declaration of Helsinki. After obtaining informed consent from the patient or the next responsible representative, patients underwent clinical evaluation and baseline biochemical tests, including hepatic biochemical tests and complete thyroid function tests, within the initial 12 hours of hospital admission. Cirrhosis was identified based on prior history of decompensations, ultrasonography, or liver biopsy evidence of cirrhosis and/or varices on endoscopy. Clinical evaluation was done by two investigators (A.V.K. and M.V.) to grade HE by West Haven criteria. All patients received recommended treatment for HE, which included identification and treatment of the underlying precipitant and disaccharidases.[5]

Statistical tests were performed using SPSS ver.29. The two groups, those who developed brain failure and those who did not, were compared using Student's *t*-test and chi-square test (or Fisher's exact test) for parametric and categorical variables, respectively. All statistical tests with $P < .05$ were considered significant. Multivariate stepwise logistic regression analysis was performed, including parameters with $P < .1$ on univariate logistic regression analysis, and the outcome was reported as odds ratio (OR).

During the study period, 276 patients were admitted, of which 112 were excluded for: acute-on-chronic liver failure (n = 54), hepatocellular carcinoma (n = 25), brain failure (n = 21), and liver transplant recipients (n = 12). One hundred sixty-four patients with a mean age of 52.41 years were included. The most common etiology of cirrhosis was MASLD in 36% of patients, followed by alcohol in 34.75%. The incidence of brain failure was 19.5% (95% confidence interval, 13.35–27.6) during a mean hospital stay of 6.71 ± 4.25 days. Baseline characteristics, including age, sex distribution, comorbidities, the reason for admission, and model for end-stage liver disease sodium score, were similar among those who developed brain failure and those who did not (Table). The most common indication for admission was infection (22%). Thirty-one percent and 15% of those who developed brain failure and those who did not develop brain failure were admitted for grade 1–2 HE, respectively. Total thyroxine levels were significantly lower in patients who developed brain failure than those who did not (5.2 ± 1.12 vs 6.24 ± 1.88 μg/ml; $P = .003$). Free T4 levels were also lower in patients with brain failure (1.1 ± 0.31 vs 1.25 ± 0.32 ng/ml; $P = .01$). However, there was no difference in the triiodothyronine (T3), free T3, and thyroid-stimulating hormone levels among the two groups. On subgroup analysis, patients with pre-existing hypothyroidism had higher thyroid-stimulating hormone and FT3 levels (but comparable T3, T4, and FT4 levels) than those without hypothyroidism (data not shown). The incidence of brain failure (9.5% vs 21%) and mortality (9.5% vs 16.8%) was, however, comparable among those with and without prior hypothyroidism. The hospital stay was longer in patients who developed brain failure (8.56 ± 4.31 vs 6.26 ± 4.13 days; $P = .006$). In-hospital mortality was higher in those who developed brain failure (28%) than those who did not (13%; $P = .03$). On univariate logistic regression analysis, grade 1–2 HE at admission (OR, 2.54 [95% confidence interval, 1.05–6.17]; $P = .04$), total thyroxine (0.64 [0.47–0.87]; $P = .005$) and free T4 (OR, 0.17 [0.04–0.71];

Table. Baseline Demographics, Clinical and Biochemical Variables at Admission

Variables	No brain failure (N = 132)	Brain failure (N = 32)	*P*
Age (years)	52.6 ± 11	51.63 ± 11.5	.65
Females	23 (17.4%)	2 (6.3%)	.17
Etiology of liver cirrhosis			
MASLD/Ethanol/Viral/Others	48/42/16/26	11/15/3/3	.33
Comorbidities			
Diabetes mellitus	56 (42.4%)	11 (34.4%)	.43
Hypertension	37 (28%)	12 (37.5%)	.29
Hypothyroidism	19 (14.4%)	2 (6.3%)	.37
Bronchial asthma	5 (3.8%)	1 (3.1%)	1
Chronic kidney disease	3 (2.3%)	0	1
Prior history of HE	9 (6.8%)	1 (3.1%)	.68
Prior TIPS	0	1 (3.1%)	.2
Admission rifaximin	46 (34.8%)	13 (40.6%)	.54
Admission lactulose	94 (71.2%)	26 (81.3%)	.37
Admission beta-blockers	42 (31.2%)	10 (31.3%)	1
Admission norfloxacin prophylaxis	10 (7.6%)	0	.21
Infection at admission	30 (22.7%)	7 (22%)	1
Reason for admission			
Infection	29 (22%)	7 (22%)	.13
AKI/dyselectrolytemia	23 (17.4%)	8 (25%)	
Anemia	12 (9.1%)	0	
Grade 1–2 HE	20 (15.2%)	10 (31.1%)	
Gastrointestinal bleed	4 (3%)	2 (6.3%)	
Ascites/pleural effusion	22 (16.7%)	2 (6.3%)	
Evaluation/procedure	11 (8.3%)	2 (6.3%)	
Liver unrelated	11 (8.3%)	1 (3.1%)	
Hemoglobin (g/dl)	9.57 ± 2.01	8.97 ± 1.42	.11
TLC (cells/mm^3)	8384.1 ± 7270.8	10,000 ± 5448.5	.24
Platelets (× 10^9/L)	130.53 ± 73.8	114.88 ± 50.6	.25
Total bilirubin (mg/dl)	6.53 ± 7.29	8.25 ± 7.21	.23
Serum albumin (g/dl)	2.76 ± 0.51	2.7 ± 0.38	.46
Serum creatinine (mg/dl)	1.3 ± 1	1.6 ± 1.18	.14
Serum sodium (meq/dl)	130.74 ± 17	131 ± 7.62	.95
T3 (triiodothyronine) (ng/ml)	0.64 ± 0.26	0.61 ± 0.25	.61
T4 (total thyroxine) (μg/ml)	6.24 ± 1.88	5.2 ± 1.12	.003
TSH (mIU/ml)	3.65 ± 5.02	2.85 ± 3.01	.39
Free T3 (pg/ml)	2.26 ± 1.06	2.23 ± 0.66	.91
Free T4 (ng/ml)	1.25 ± 0.32	1.1 ± 0.31	.01
Ammonia (μmol/L)	81.97 ± 52.67 (n = 33)	87.71 ± 33.94 (n = 24)	.64
MELD NA	22.25 ± 7	24.2 ± 5.42	.14
Duration of hospital stay (days)	6.26 ± 4.13	8.56 ± 4.31	.006
In-hospital mortality	17 (13%)	9 (28%)	.03

AKI, acute kidney injury; MELD NA, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt; TLC, total leukocyte counts; TSH, thyroid-stimulating hormone.

P = .01) predicted development of brain failure while on multivariate logistic regression analysis, only total thyroxine levels predicted the development of brain failure (OR, 0.64 [0.47–0.88]; P = .005).

The relationship between liver and thyroid function is bidirectional. While thyroid hormones regulate glucose and lipid metabolism through the liver, the liver is the source of thyroid-binding globulin and is involved in thyroid hormone conjugation, biliary excretion, and deiodination of T4 to T3 and reverse T3 (rT3). Patients with cirrhosis are in a sick euthyroid state (low T4, FT3, and high rT3) due to reduced deiodinase type 1 activity in the liver and increased deiodinase type 3.[6,7] This adaptive state preserves liver function and total body protein stores by reducing the basal metabolic rate within hepatocytes.[8] Lower thyroxine levels may, therefore, indicate advanced liver disease with lower levels of bound and free T4.[9] Although both free T4 and thyroxine levels can aid in the prediction of brain failure, total thyroxine assessment is universally available and more valuable.

There are a few differences between the current study and the previous study by Bajaj et al. apart from the racial differences (pure Asian in our cohort). We included patients with hypothyroidism, which was not included in the previous study; secondly, the most dominant etiology was MASLD, unlike alcohol in the previous study. Despite these differences, thyroxine levels could predict the development of brain failure in patients with cirrhosis admitted to the hospital. This simple economical biomarker is an excellent tool for the prediction of HE. A major limitation of the current study is that we did not assess other metabolites, which could have made our study more robust. Also, we included only inpatients, and whether such an association exists in outpatients needs to be assessed. Lastly, we did not perform specific tests for minimal HE at admission, and all patients did not undergo ammonia level assessment, which may also have identified patients at risk of brain failure. Although strict control of thyroid function is desired, it is unknown whether prophylactic thyroxine supplementation, even in euthyroid cirrhosis patients, may prevent HE.[10]

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Abbreviations used in this paper: **AKI, acute kidney injury; HE, hepatic encephalopathy; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD NA, model for end-stage liver disease; OR, odds ratio; TIPS, transjugular intrahepatic portosystemic shunt; TLC, total leukocyte counts; TSH, thyroid-stimulating hormone**

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