Depression and Insomnia Are Closely Associated with Thyroid Hormone Levels in Chronic Hepatitis B

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Background: Depression and insomnia in chronic hepatitis B (CHB) patients affect the quality of life, disease diagnosis, and mortality. CHB patients are more likely to have psychological disorders, but the underlying mechanisms have not been elucidated. This study investigated the incidence of depression in patients with CHB and sought to identify risk factors for depression and insomnia in these patients, focusing on changes in liver function and thyroid hormone levels.

Material/Methods: This cross-sectional cohort study used the Hamilton Depression Scale and Athens Insomnia Scale to assess the depressive and insomnia states, respectively, of 209 CHB patients. Liver function, thyroid hormone levels, hepatitis B surface antigen, hepatitis B e-antigen, and hepatitis B virus-deoxyribonucleic acid load were evaluated. Liver cirrhosis was assessed by imaging (color Doppler ultrasound and computed tomography). A multivariate logistic regression model was used to analyze the correlation among various factors and depression and insomnia.

Results: Subclinical and clinical depressive states were found in 23.9% and 5.3% and subclinical and clinical insomnia in 11% and 35.4% of patients, respectively. Depression and insomnia severity were significantly correlated with low FT3 (<3.5 mol/L). The odds ratios of low FT3 for subclinical and clinical depression and clinical insomnia were 3.07 (95% confidence interval (CI), 1.248–7.568), 7.85 (95% CI, 1.839–33.547), and 3.91 (95% CI, 1.417–10.789), respectively.

Conclusions: CHB patients are prone to depression and insomnia. FT3 reduction may be a risk factor for depression and insomnia. In clinical settings, more attention needs to be paid to the mental state of patients with FT3 reduction.

MeSH Keywords: Depression • Hepatitis B, Chronic • Risk Factors • Sleep Initiation and Maintenance Disorders

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Background

Chronic diseases often cause serious psychological problems, including depression, anxiety, and sleep disorders. Severe mental disorders in patients with chronic diseases can seriously affect the health-related quality of life (QOL) [1]. More than 240 million individuals worldwide are infected with chronic hepatitis B virus, and because cure rates are low, most patients will require therapy indefinitely [2], which imposes a serious psychological burden on CHB patients. An increasing number of researchers have started focusing on mental health problems in chronic hepatitis B (CHB) patients. Atesci et al. [3] assessed the incidence of mental disorders in 43 hepatitis B virus (HBV) carriers and 43 healthy controls using the Beck depression scale. They found that HBV carriers were more susceptible to mental disorders than normal people (30.2% *vs.* 11.6%). Chinese researchers evaluated the mental symptoms of 114 patients with post-hepatitis B cirrhosis and found 33.3% of them had emotional disorders [4]. The incidence of mental disorders in hepatitis B patients is significantly higher than that in normal persons, but related research has focused on the epidemiological investigation of mental health problems in hepatitis B patients. Some researchers attribute mental health problems in hepatitis B patients to personal and social factors [5,6], but few have studied how HBV affects the occurrence of mental disorders in these patients.

Psychiatrists generally believe that thyroid hormones are closely linked to mental disorders. Patients with depression have a higher incidence of hypothyroidism, and patients with hypothyroidism have a higher incidence of depression [7,8].

The liver plays a major role in thyroid hormone metabolism, especially in its conjugation, excretion, and deiodination [9]. Evidence shows that chronic liver disease is linked to thyroid hormone levels [10–12]. The most frequent change in thyroid hormone levels in plasma is decreased serum triiodothyronine (T3) and free T3 (FT3) concentration, which is reported to be associated with the severity of hepatic dysfunction [11,12]. However, the level of thyroid hormone in CHB patients with depression and insomnia is still under-investigated. Hence, the present study investigated the incidence of depression and insomnia in CHB patients and sought to identify the risk factors for these disorders in CHB patients by evaluating thyroid hormone levels (FT3, FT4, Thyroid stimulating hormone (TSH)), liver function parameters, and the presence of liver cirrhosis.

Material and Methods

Patients

A prospective cohort of 209 patients with chronic hepatitis B was recruited from the Department of Infectious Diseases of the Affiliated Hospital of Qingdao University between June 2017 and May 2018. Patients who met the diagnostic criteria for hepatitis B and cirrhosis of the liver according to consensus recommendations of the Asian Pacific Association for the Study of the Liver in 2015 were included [13]. The exclusion criteria were as follows: mental illness, severe diabetes, thyroid disorders or other endocrine system illness; drug addiction and alcohol dependence; pregnancy or lactation; hepatic encephalopathy; unwillingness to cooperate following communication with the medical staff; history of psychiatric drug use in the previous 2 weeks or a family history of mental illness; co-infection with other viruses (hepatitis A, C, E, or human immunodeficiency virus); other liver diseases (Wilson's disease, alcoholic liver disease, or auto-immune diseases); hepatocellular carcinoma; renal insufficiency; or serious diseases in other organ systems.

The study included 318 patients for the first time, including 284 inpatients and 34 outpatients. Among them, 14 outpatients were excluded because they refused to complete the imaging examination, and 6 cases were excluded because they could not complete the psychological assessment. Of the inpatients, 22 were found to have tumors or suspected tumors, 12 were unable to complete psychological assessment, 17 were recently treated with pegylated interferon therapy, 5 were eventually diagnosed with thyroid disease, 8 were diagnosed with hepatic encephalopathy, and 26 also had other chronic liver diseases, and these patients were excluded. Finally, 20 outpatients and 189 inpatients were enrolled.

The study was carried out according to the World Medical Association Declaration of Helsinki. The study protocol was approved by the Medical Ethics Committee of the Affiliated Hospital of Qingdao University. The participants provided written informed consent before participation in this study.

Evaluation of psychiatric characteristics

The Hamilton Depression Scale [14] is the most commonly used scale for clinical assessment of depressive symptoms. This study used the version containing 24 items, including various symptoms involved in depression. The majority of these symptoms were given a severity rating ranging from not present (score 0) to very severe (score 4). Some symptoms were given a severity rating ranging from not present (score 0) to severe (score 2). A total score of 0–6 is considered normal, a total score of 7–19 indicates subclinical depression, and a total score of ≥20 indicates clinical depression.

The Athens Insomnia Scale (AIS) was used to measure sleep quality of subjects. It is built on the International Classification of Diseases 10 criteria and was validated by Soldatos et al. [15]. The AIS is a self-administered inventory consisting of 8 items: 5 items rate difficulty with sleep induction, awakening during the night, early morning awakening, total sleep time, and overall quality of sleep, and 3 items pertain to the next-day consequences of insomnia. Each symptom was given a severity rating ranging from not present (score 0) to very severe (score 3). A total score of 0–3 is considered normal, a total score of 4–6 indicates subclinical insomnia, and a total score of >6 indicates clinical insomnia.

Each patient was jointly examined and assessed by 2 medically trained professionals. The scores were independently assigned, and the consistency was above 90%.

Demography and clinical characteristics

We recorded sex, age, body mass index (BMI), marital status, education level, duration of hepatitis B infection, current smoking, and alcohol consumption (alcohol intake in 2 weeks equivalent to ethanol content >80 g/d is considered alcoholism). Blood pressure and blood glucose status after admission were used to confirm the presence of hypertension and diabetes, respectively.

Clinical characteristics: In all patients, fasting venous blood samples were collected at 8 am during hospitalization. Measurements of biochemical parameters were routinely performed in the Central Clinical Laboratory of the Affiliated Hospital of Qingdao University. Serum thyroid hormone levels (FT3, FT4, and TSH) were monitored by chemiluminescence. In addition, chemiluminescence was utilized to detect HB surface antigen and HB e-antigen (HBeAg). HBV-DNA was quantitatively assessed by real-time quantitative polymerase chain reaction. Liver cirrhosis was evaluated by imaging (color Doppler ultrasound and computed tomography).

Statistical analysis

Data analysis was performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). Clinical characteristics of the total population were summarized using standard descriptive statistics. Continuous values are expressed as mean ± standard deviation, and categorical values are presented as count and proportions. Between-group comparisons involving categorical data were performed using χ^2 statistics corrected for continuity (Fisher's exact test when appropriate). One-way analysis of variance was used to compare and calculate continuous data between groups. When univariate variables showed statistically significant effects ($P<0.05$), they were included in the multivariate logistic regression analysis. For all analyses, $P<0.05$ was considered to indicate a statistically significant result.

Results

A total of 209 CHB subjects participated in the study, including 139 men (66.5%) and 70 women (33.5%). Table 1 presents the results of a general analysis of the degree of depression and CHB subjects. Of the 209 subjects, 50 had subclinical depression (23.9%) and 11 had clinical depression (5.3%). General characteristics included sex, age, BMI, marital status, education level, smoking, drinking, diabetes, liver cirrhosis, and hypertension.

Table 2 lists the results of a univariate analysis of the degree of depression and CHB subjects. The levels of total bilirubin (TBil), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in the subclinical and clinical depression groups were higher than those in the normal group ($P<0.05$). The subclinical and clinical depression groups had lower FT3 (FT3 <3.5 mol/L) and the FT3 average value was lower ($P<0.001$). There was no significant difference between depression status and cirrhosis, HBeAg positivity, HBV-DNA, FT4, and TSH.

Table 3 shows the analysis results of the general characteristics of subjects with insomnia and CHB. Of the 209 subjects, 23 had subclinical insomnia (11%) and 74 had clinical insomnia (35.4%). Elderly patients were more likely to have insomnia ($P=0.036$). There was no significant difference in gender, BMI, marital status, education level, smoking, drinking, diabetes, liver cirrhosis, and hypertension.

Table 4 presents the univariate analysis results of the degree of insomnia and CHB subjects. The TBil, AST, and ALT in the clinical insomnia group were higher than those in the normal group ($P<0.05$). The clinical insomnia group had a lower FT3 (FT3<3.5 mol/L) and a lower FT3 average value ($P<0.001$). There was no significant difference between insomnia and cirrhosis, HBeAg positivity, HBV-DNA, FT4, and TSH.

Table 5 shows the multivariate logistic regression analysis results of depression and insomnia. Parameters showing statistical significance after a univariate analysis were included in the multivariate logistic regression analysis. The results showed a weak correlation between depression and TBil. Subclinical and clinical depression OR were 1.01 (95% confidence interval (CI), 1.001–1.027) and 1.02 (95% CI, 1.001–1.034), respectively. However, low FT3 (FT3 <3.5 mol/L) had a strong correlation with depression; the subclinical depression OR was 3.07 (95% CI, 1.248–7.568) and clinical depression OR was 7.85 (95% CI, 1.839–33.547). There was a strong correlation between clinical insomnia and low FT3, with an OR of 3.91 (95% CI, 1.417–10.789), and a weak correlation with TBil, with an OR of 1.92 (95% CI, 1.001–1.030).

Table 1. Relationship between depressive symptoms and patient characteristics in chronic hepatitis B patients.

| Variables | Depressive symptoms | | | p |
	None (N=148)	Subclinical (N=50)	Clinical (N=11)	
Male	102 (68.9%)	30 (60.0%)	7 (63.6%)	0.502
Age (years)	43.0±13.0	44.4±14.7	50.6±11.1	0.173
Married	139 (93.9%)	43 (86.0%)	10 (90.9%)	0.207
BMI (kg/m²)	24.8±3.6	25.0±2.1	24.8±3.3	0.978
Alcohol consumption	33 (22.3%)	9 (18.0%)	4 (36.4%)	0.407
Smoking	42 (28.4%)	7 (14.0%)	3 (27.3%)	0.124
Hypertension	19 (12.8%)	7 (14.0%)	0 (0.0%)	0.428
Diabetes mellitus	4 (2.7%)	5 (10.0%)	0 (0.0)	0.069
Liver cirrhosis	56 (48.2%)	22 (45.5%)	5 (44.0%)	0.542
Child-Pugh A	46 (82.1%)	13 (59.1%)	3 (60.0%)	0.080
Child-Pugh B	6 (10.7%)	5 (22.7%)	0 (0.0%)	0.247
Child-Pugh C	4 (7.1%)	4 (18.2%)	2 (40.0%)	0.057
Education (years)	12.1±3.2	10.6±4.1	12.1±3.5	0.355
Illness time (years)	11.8±11.3	18.1±6.1	11.6±9.2	0.092

BMI – body mass index.

Table 2. Laboratory parameters by depression status in chronic hepatitis B patients.

| Variables | Depressive symptoms | | | p |
	None (N=148)	Subclinical (N=50)	Clinical (N=11)	
ALT (U/L)	124.2±144.8	185.6±234.2	257.9±121.3*	0.008
AST (U/L)	81.9±108.7	138.0±216.6*	199.2±76.3*	0.004
HBV-DNA (IU/mL)	4.6E8±2.4E8	2.3E8±6.1E8	5.2E7±1.3E8	0.701
HBeAg positive	91 (61.5%)	32 (64.0%)	9 (81.8%)	0.399
TBil (µmol/L)	24.4±26.0	49.8±76.3*	80.9±47.1*	0.000
FT3 (pmol/L)	4.6±1.0	4.1±1.0*	3.5±0.9*	0.000
FT4 (pmol/L)	14.4±2.2	14.6±2.7	15.0±2.3	0.858
Low FT3 (<3.5 µmol/L)	14 (9.5%)	15 (30.0%)*	6 (50.0%)*	0.000
TSH (µIU/mL)	2.0±1.9	2.1±2.2	2.0±0.6	0.970
TSH reduction (<0.55 mIU/L)	4 (2.0%)	5 (8.0%)	0 (0.0%)	0.071
TSH rise (>4.78 mIU/L)	4 (2.7%)	4 (8.0%)	0 (0.0%)	0.197

* P<0.05 *vs.* none. ALT – alanine aminotransferase; AST – aspartate aminotransferase; HBeAg – hepatitis B e-antigen; TBil – total bilirubin; TSH – thyroid stimulating hormone.

Discussion

In previous studies, the prevalence of mental disorders in CHB patients was 10–40% [16]. Similar results were noted in this study: subclinical and clinical depression had a prevalence of 29.2%, and subclinical and clinical insomnia had a prevalence of 46.4%. Moreover, the prevalence of mental disorders in CHB patients is much higher than that in the normal population. After multiple logistic regression analysis, we found a strong correlation of the decrease in FT3 levels (<3.5 mol/L) with depression and insomnia, and a weak correlation with increased TBil values. To the best of our knowledge, this is the first study

Table 3. Relationship between insomnia symptoms and patient characteristics in chronic hepatitis B patients.

| Variables | Insomnia symptoms | | | p |
	None (N=112)	Subclinical (N=23)	Clinical (N=74)	
Male	77 (68.8%)	18 (78.3%)	44 (59.5%)	0.189
Age (years)	42.0±12.8	41.8±13.4	**46.9±14.0***	**0.036***
Married	107 (95.5%)	20 (87.0%)	65 (87.8%)	0.113
BMI (kg/m²)	25.1±3.4	25.4±3.0	24.3±3.3	0.176
Alcohol consumption	22 (19.6%)	7 (30.4%)	17 (23.0%)	0.507
Smoking	35 (31.3%)	4 (17.4%)	13 (17.6%)	0.073
Hypertension	16 (14.3%)	1 (4.3%%)	9 (12.2%)	0.419
Diabetes mellitus	3 (2.7%)	1 (4.3%)	5 (6.8%)	0.407
Liver cirrhosis	42 (37.5%)	10 (43.5%)	30 (40.5%)	0.832
Child-Pugh A	34 (81.0%)	8 (80.0%)	20 (66.7%)	0.358
Child-Pugh B	6 (14.3%)	1 (10.0%)	4 (13.3%)	0.938
Child-Pugh C	2 (4.8%)	1 (10.0%)	6 (20.0%)	0.124
Education (years)	12.1±3.4	12.7±3.6	11.6±3.5	0.371
Illness time (years)	11.5±9.2	10.1±9.4	13.3±10.6	0.296

* P<0.05 *vs.* none; BMI – body mass index.

Table 4. Laboratory parameters by insomnia status in chronic hepatitis B patients.

| Variables | Insomnia symptoms | | | p |
	None (N=112)	Subclinical (N=23)	Clinical (N=74)	
ALT (U/L)	114.9±126.4	194.4±222.5	177.8±206.1*	0.018
AST (U/L)	69.4±72.4	103.5±104.1	149.5±209.9*	0.001
HBV-DNA (IU/mL)	5.9E8±2.8E8	2.3E8±6.0E8	1.4E8±4.3E8	0.338
HBeAg positive	67 (59.8%)	12 (52.2%)	53 (71.6%)	0.135
TBil (μmol/L)	22.3±22.6	34.7±43.6	50.0±65.0*	0.000
FT3 (pmol/L)	4.7±1.0	4.5±0.9	4.0±1.0*	0.000
FT4 (pmol/L)	14.4±2.2	14.6±2.7	15.0±2.3	0.858
Low FT3 (<3.5 μmol/L)	7 (6.3%)	4 (17.4%)	24 (32.4%)*	0.000
TSH (μIU/mL)	2.1±2.1	2.0±1.0	2.0±1.9	0.995
TSH reduction (<0.55 mIU/L)	3 (2.7%)	2 (8.7%)	4 (5.4%)	0.366
TSH rise (>4.78 mIU/L)	3 (2.7%)	3 (13.0%)	3 (4.1%)	0.082

* P<0.05 *vs.* none. ALT – alanine aminotransferase; AST – aspartate aminotransferase; HBV-DNA – hepatitis B virus-deoxyribonucleic acid; HBeAg – hepatitis B e-antigen; TBil – total bilirubin; TSH – thyroid stimulating hormone.

reporting that depression and insomnia in CHB patients are associated with thyroid hormone and liver function.

In this study, we used AIS to assess insomnia in CHB patients, and we found that 46.4% of CHB patients were affected by insomnia; moreover, insomnia was almost always found in patients with depression. Insomnia is part of the mood disorder symptomatology and some anxiety disorders. Insomnia may be the most obvious manifestation of this disease, and its presence or absence do not change the evolution of the psychiatric disorder [17].

Table 5. Multivariate logistic regression analysis of variables related to depression and insomnia.

Variables		Subclinical		Clinical	
		OR (95% CI)	P	OR (95% CI) P	P
Depression	ALT	–		1.00 (0.996–1.008)	0.556
	AST	1.00 (0.993–1.004)	0.613	1.00 (0.990–1.004)	0.447
	TBil	1.01 (1.001–1.027)	0.031	1.02 (1.001–1.034)	0.032
	Low FT3	3.07 (1.248–7.568)	0.015	7.85(1.839–33.547)	0.005
Insomnia	ALT	–		1.00 (0.990–1.001)	0.113
	AST	–		1.00 (1.000–1.016)	0.066
	TBil	–		**1.02 (1.001–1.030)**	0.042
	Low FT3	–		**3.91(1.417–10.789)**	0.008
	Age	–		1.00 (0.975–1.031)	0.853

ALT – alanine aminotransferase; AST – aspartate aminotransferase; CI – confidence interval; OR – odds ratio; TBil – total bilirubin.

As early as 60 years ago, psychologists discovered that depression is associated with hypothyroidism [18]; and 1–4% of patients with affective disorders have a significant hypothyroidism, and 4–40% have subclinical hypothyroidism (SCH). Compared to those with general depression, patients with refractory depression are more likely to have SCH [8].

The liver plays an essential role in the metabolism of thyroid hormones. First, the liver can produce type I and III deiodinated enzymes. More than 80% of tetraiodothyronine (T4) is 5' deiodinated and converted to triiodothyronine (T3) by type I deiodinase [19], and the main effect of type III deiodinase is to inactivate T3 [20]. The decrease in total T3 may be due to a decrease in type I deiodinated enzyme activity in patients with chronic liver disease. Second, the liver is where synthesis of thyroid hormone-binding protein occurs. Notably, thyroxine-binding globulin is negatively correlated with Child-Pugh score [9,11]. The decrease of thyroid hormone level aggravates liver inflammation and fibrosis by regulating liver lipid metabolism, which further leads to liver injury [21]. More than 99% of thyroid hormones in the plasma bind to thyroid hormone-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and albumin (Alb). The decreasing protein-binding ability results in decreased T3 after liver injury. Some researchers believe that although the total T3 of patients with liver disease has changed, TSH and T4 are still at a stable level, and the change in T3 level may be an adaptation mechanism to reduce heat demand by reducing basal metabolism [12].

FT3 and FT4 have important physiological effects in the body: FT3 accounts for 0.3% of TT3 and FT4 accounts for 0.03% of TT4. TT3 and TT4 concentrations often change with the concentration of TBG, TBPA, and Alb in the blood. Therefore, the present study measured FT3 and FT4 as observation indexes.

Notably, 15.8% of patients with CHB had reduced FT3, while the reduction in FT3 is more obvious in patients with mental disorders and insomnia. Therefore, the reduction in FT3 in CHB patients can be considered closely related to mental disorders and insomnia. Although the total T3 of patients with liver disease changed, TSH and T4 were still at a stable level, indicating that hypothalamic-pituitary-thyroid axis function was not impaired in this group of patients, and the reduction in FT3 may be the common result of impaired liver function and body compensation.

Biological processes and pathways of depression generally involve inflammation, oxidation, and nitrosative stress pathways; neurotransmitter systems; neurotrophins; and regulation of neurogenesis and the hypothalamic-pituitary-adrenal axis [22]. Because of the high metabolic and low antioxidant characteristics of the brain, oxidative and nitrosative stress pathways are considered the most crucial pathophysiological factors [23]. Bilirubin, as the final metabolite of hemoglobin, is a strong antioxidant, but also has neurotoxicity and can easily spread through the blood-brain barrier [24]. Unconjugated bilirubin has been proved to cause neurotoxicity and brain cell death [25]. Therefore, 2 conflicting results have been observed in previous studies. Some studies have shown that the decline in serum bilirubin is a risk factor for depression [26], but there is strong evidence that a rise in bilirubin level is a risk factor for depression [24]. Meanwhile, Saleh et al. found that the most important factor affecting sleep disturbance in cirrhosis patients is the increase in serum bilirubin [27]. In a present study, multivariate analysis showed a weak correlation of TBil levels with subclinical and clinical depression, and a weak correlation with clinical insomnia.

This study has some limitations. First, the analysis was limited by its cross-sectional design, and not all potential confounding factors were controlled. Second, the assessment of liver cirrhosis was not confirmed by histology. The imaging evaluation may have ignored some patients with early cirrhosis, and previous studies have shown that depression in patients with chronic liver disease is closely related to the degree of cirrhosis [4,28]. Further prospective studies using histology as a standard for cirrhosis assessment and regular follow-up assessments are needed to validate our results.

Conclusions

In conclusion, the incidence of depression and insomnia in CHB patients is very high. Mental disorders have a significant adverse effect on the treatment and prognosis of chronic diseases and deserve attention. We propose that the assessment and treatment of mental disorders should be focused on during the active treatment of primary liver diseases. This study indicates that depression and insomnia in CHB patients are associated with thyroid hormone levels. The decrease in FT3 may be a risk factor for depression and insomnia in CHB patients. In clinical settings, more attention needs to be paid to the mental state of patients with FT3 reduction.

Acknowledgements

Conflict of interest

None.

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