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Depression in autoimmune hepatitis: a need for detailed psychiatric assessment

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INTRODUCTION

Autoimmune hepatitis (AIH) is a progressive liver disease, occurring more frequently in females, which, if left untreated, leads to liver cirrhosis and hepatic failure [1]. Current therapies are based on long-term immunosuppression, which induce remission in a majority of patients; however, the risk of subsequent relapses is high. Adherence to the therapy is one of the crucial factors for achieving clinical success [2].

Recent studies have demonstrated that patients with AIH suffer from a substantially diminished health-related quality of life [3–5]. In particular, depression has emerged as an under-estimated factor affecting the well-being of patients with AIH [6]. Unfortunately, depression is rarely assessed in everyday clinical practice. The Patient Health Questionnaire-9 (PHQ-9) and the Hospital Anxiety and Depression Scale (HADS) are simple screening tools, which have been successfully applied in AIH and indicated patients for further evaluation. They do not, however, permit a precise assessment of the condition. Indeed, the final diagnosis of depression requires the appraisal of depression etiology, duration of symptoms, effect on daily activities, psychiatric history, and other factors that are not considered in the screening tools.

Given the above, we performed an extended psychiatric assessment which involved a detailed psychiatric evaluation, a battery of screening tests, and a structured interview (M.I.N.I.), focusing on patients with AIH who previously presented the highest scores in the depression screening test in our center.
MATERIALS AND METHODS

We prospectively included adult patients with AIH from our previous study [5] who had screened positively for moderately severe depression (>15 points on the PHQ-9 test).

According to Levis et al. [7], this cut-off allows exclusion of major depression in 96% of patients. None of the included patients had signs of decompensated liver cirrhosis, hepatic encephalopathy, malignancies, previously diagnosed psychiatric diseases, or complained about side-effects of the AIH drugs. The study flow-chart is presented in Figure 1.

PSYCHIATRIC ASSESSMENT

A psychiatric assessment, comprised of psychiatric consultation (documented with a standard Massachusetts General Hospital Psychiatric Consultation Note [8]) and a battery of validated tests, namely: the Alcohol Use Disorders Identification Test (AUDIT), the Generalized Anxiety Disorder 7 (GAD-7), which were included in the Stanford Integrated Psychosocial Assessment for Transplant final score (SIPAT), and the Mini-International Neuropsychiatric Interview (M.I.N.I.)

Generalized Anxiety Disorder-7 (GAD-7)

GAD-7, stemming from Primary Care Evaluation of Mental Disorders screening tool (PRIME-MD), is a self-administered screening test for core anxiety symptoms, primarily designed as a measure to screen for Generalized Anxiety Disorder, but also having sufficiently good operating characteristics for three other anxiety disorders: panic disorder, social anxiety disorder, and post-traumatic stress disorder [9]. The severity of anxiety is assessed by assigning 0, 1, 2, or 3 to the response categories “not at all”, “several days”, “more than half of the days”, or “nearly every day”, respectively, with a total score ranging
from 0 to 21. The recommended cut-off point for further evaluation is a score of 10 or greater [9].

The Mini-International Neuropsychiatric Interview (M.I.N.I.)

M.I.N.I. is a structured psychiatric interview developed by Sheehan et al. [10], allowing psychiatric diagnosis according to DSM-IV and ICD-10 psychiatric criteria, with good accuracy and reliability.

Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT screening tool was used to exclude alcohol use disorders overlapping with depressive symptoms, anxiety, and liver disfunction [11]. Although patients with AIH are not commonly diagnosed with alcohol abuse or dependency, some of them are not committed to absolute abstinence after AIH diagnosis, which may shape the course of the disease and influence psychiatric symptoms, and a differential diagnosis should be documented. AUDIT is a 10-item tool, developed by the World Health Organization (WHO), to assess alcohol consumption, drinking behaviours, and alcohol-related problems. Patients are also encouraged to declare their alcohol consumption in terms of standard drinks. A chart illustrating the approximate number of standard drinks in different alcohol beverages is included for reference. A total score of 8 or more is considered to indicate hazardous or harmful alcohol use.
Stanford Integrated Psychosocial Assessment for Transplant (SIPAT)

The SIPAT scale was developed by Maldonado et al. [12] as a complex and thorough tool, integrating the assessment of a patient’s understanding of the disease, adherence, social support, and readiness for treatment and a psychiatric risk screening that include stratified PHQ-9 (alternatively Beck Depression Inventory score), GAD-7 scores, Mini-Mental State Examination score, AUDIT and a screening for illicit drug related problems. The scoring allows for stratification of potential liver transplant recipients into excellent, good, minimally-accepted, poor, and high-risk candidates, but also suggests recommendations for re-mediation measures and re-assessment.

CLINICAL EVALUATION

Routine liver function tests and liver stiffness measurements using 2D-Real Time Shear Wave Elastography were performed. The diagnosis of cirrhosis was based on histology, elastography, and/or imaging studies. The local ethics committee approved the study protocol (KB/128/2015), and written consent was obtained from all participants.

STATISTICS

Data were presented as mean ± standard deviation (SD) and/or median and range when appropriated, for continuous variables. The Kolmogorov-Smirnov normality test was used to examine the distribution of quantitative variables, which revealed non-parametrical distribution. Data were analysed with Dell Statistica, version 13 (Dell Inc. Tulsa, USA).
RESULTS

Fourteen patients comprising 10% of the total number of 140 patients included into our previous study [5] had results suggesting moderately severe depressive symptoms in the screening tests. Four patients were excluded from further analysis: one had developed a decompensation of his liver function, the second was diagnosed with the hepatocellular carcinoma (HCC), and the two other patients were transplanted before the psychiatric assessment. The clinical data and results from the psychiatric evaluation are presented in the Supplementary materials (Table S1). None of the patients had a flare of AIH. The detailed psychiatric assessment consultations revealed a positive diagnosis of depression (present, past, or recurrent) in six patients (60%), as well as anxiety- or stress-related disorders in two patients (20%). Finally, six patients (60%) were recommended antidepressive agents (selective serotonin or serotonin and norepinephrine reuptake inhibitors) and were assigned a psychiatric follow-up. It is worth noting that nine patients had never sought psychiatric assistance before. Of interest, two patients who had undergone liver transplantation and were excluded from the cohort had no signs of depression in the follow-up but had been diagnosed with adjustment disorders (ICD-10: F43.2).

DISCUSSION

To the best of our knowledge, this is the first study, which estimates the prevalence of depression in AIH using full psychiatric check-up. We performed a thorough psychiatric assessment of patients who screened positively for moderately severe depression in a simple and commonly used questionnaire, the PHQ-9. This assessment showed that six out of ten patients had depression, which required medical therapy. Two of them were diagnosed with an anxiety- or stress-related disorder(s) as concomitant comorbidities. These results are in line with a recently published meta-analysis, which showed that a higher cut-off of the PHQ-9
(e.g., >15 points) could correctly rule out patients with major depression, but could also result in a false positive in 39% of the positively-screened patients [7]. The detailed psychiatric interview results confirmed the mentioned false positive rate using a higher cut-off of the PHQ-9, in the AIH setting. A lower specificity of the PHQ-9 was described in younger populations (7), which corresponds well with our cohort of patients and may have affected the final results.

These findings suggest that the current available screening methods might not be adequate for estimating the real extent of depression and other psychiatric disorders in the setting of AIH. They could also explain the discrepancy in the results of positive screening for depression in published cohorts, which range from 5.5% to 29%, depending on the cohort [6].

Overall, the herein-presented results further underscore the fact that presumed depression, detected with basic screening modalities, requires special attention in patients with AIH. It should be followed up by thorough evaluation since therapeutic intervention may be required in the majority of the identified subjects. This is of particular importance for younger patients, as depression affects not only their well-being, but also their adherence to treatment. The latter may detrimentally impact the outcome of therapy [2]. To accomplish this task, a close co-operation between hepatologists and psychiatrists is needed; importantly, dedicated screening tools must be developed and validated in the near future.
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**Author Contributions:** MJ, MM provided acquisition of the data; MJ, EW, MM, JRW, MK and PM analysed and interpreted the data; MM provided a psychiatric assessment; PM designed and supervised the study; all authors participated in drafting the first version of the manuscript which was edited by PM. PM is the guarantor of the article. All authors read and approved the final version of the manuscript.
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Figure 1. Flow-chart of the study.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; GAD-7, Generalized Anxiety Disorder 7; HCC, Hepatocellular Carcinoma; PHQ-9, Patient Health Questionnaire-9; SIPAT, Stanford Integrated Psychosocial Assessment for Transplant. The diagnoses according to ICD-10 were provided in brackets. * - Comorbidities diagnosed in two patients: one with F33 and one with F32, according to ICD-10.