UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA

DOCTORAL SCHOOL

CLINICAL AND EVOLUTIVE PECULIARITIES IN PATIENTS WITH DEPRESSIVE DISORDER AND CHRONIC HEPATITIS

ABSTRACT

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INTRODUCTION

Major depressive disorder, major depression, or simply depression continues to be one of the biggest challenges in psychiatry from the point of view of depressive symptoms and socio-professional reintegration of patients and the costs that these objectives involved.

The role that biological systems play in the etiopathogenesis of depression, implications and correlations between depressive disorder and somatic diseases that could change the clinical treatment or could influence some particular aspects of evolution are still unknown, especially in chronic hepatitis, being well known the high prevalence of psychiatric symptoms, especially depressive ones in chronic hepatitis [1, 2].

Recent studies have highlighted the close link between the hypothalamic-pituitary-adrenal axis (HPA) and the inflammatory response in chronic hepatitis. Also, there is a change in the thyroid-parathyroid system closely related to serotonin. Cytokines produced changes in serotonin 5-HT receptors and tryptophan, the precursor of serotonin, thus proving a role in development of the disorder, depressive [3].

In addition to all the data related to liver pathology, changes in brain monoamines, psychosocial factors related to each individual, we found the depressive effect of antiviral medication. Recent studies have shown that up to 25% of patients with chronic hepatitis B and C treated with interferon have a major depressive episode during or after antiviral therapy [4]. The mechanisms by which anti-viral therapy, and in particular interferon, inducing depressive symptoms are not yet fully understood.

There are situations under which interferon may have an effect on the glucocorticoid and serotonin 5-HT1A receptors as well as on the secretion of ACTH, plasma cortisol, and interleukin-6, which causes symptoms of depression [5, 6].

We believe that the evaluation of clinical, developmental and therapeutic response in patients with major depression and chronic hepatitis B and C, requires a complex analysis of the study cases in order to highlight the potential risk factors that allow a differentiated therapeutic approach, and creating a system of preventive measures. Both major depressive disorder and chronic viral hepatitis are real public health issues.

METHODS

Hypothesis

Major depressive disorder is itself a real public health problem, both by hospital and treatment costs and by the socio-economic data for absenteeism at work. If a medical condition is added to major depression, chronic viral hepatitis in our case, we can say that the implications are so complex that we could hardly make a correct estimate of their magnitude [7, 186]. Starting from these premises, the study of peculiarities of therapeutic response to antidepressant medication and their correlation with the evolution of the disease would allow us to evolve some risk factors for depressive disorder in patients with chronic hepatitis, in order to improve therapeutic strategies in the field.

Objectives

1. Highlighted the clinical features of depressive disorder in patients with chronic hepatitis hospitalized in Psychiatry Section III of Psychiatric Hospital "Dr. Gheorghe Preda" Sibiu and quality assessment of response to antidepressant medication.
2. Identification of risk factors linked to major depressive disorder or chronic viral hepatitis, involved in unfavorable evolution in these patients.

Retrospective-prospective study of patients hospitalized in the Psychiatry Section III of Psychiatric Hospital "Dr. Gheorghe Preda" Sibiu, with a diagnosis of major depressive disorder, between 1 January 2010 - 31 December 2012, previously diagnosed, investigated and treated for chronic hepatitis (B or C virus) in Sibiu County Hospital.

Data sources: observation sheets of the inpatients from Psychiatry Section III of Psychiatric Hospital "Dr. Gheorghe Preda" Sibiu, observation sheets of patients with chronic hepatitis hospitalized in Sibiu County Hospital, psychological examinations and laboratory results.

Items Registered: Socio-demographic (age, sex, area of residence, educational level), clinical and evolutionary indicators (year of onset of major depression, number of depressive episodes, comorbid psychiatric disorders, comorbid somatic disorders, type of chronic viral hepatitis, year when diagnosis of chronic hepatitis was established, class of antidepressants used during hospitalization, adjunctive medication, scores on assessment scales, treatment with interferon, liver histopathology).

Working tools: Hamilton Depression Rating Scale (HAM-D17), Montgomery-Asberg Depression Rating Scale (MADRS), Mini-Mental Scale Evaluation (MMSE).

Study group N=121

Based on the inclusion and exclusion criteria it was constituted the study group comprised of 121 patients (N=121) divided into two subgroups: N1= 63 patients hospitalized in Psychiatry Section III of Psychiatric Hospital "Dr. Gheorghe Preda" Sibiu with a diagnosis of major depressive episode or recurrent depressive disorder according to ICD 10 and/or DSM IV TR , between 1 January 2010 – 31 December 2012, patients who were previously diagnosed and treated for chronic viral hepatitis (B virus or C) in the Sibiu County Hospital (1 January 2008 – 31 December 2010) and N2=58 patients diagnosed with major depressive episode or recurrent depressive disorder according to ICD 10 and/or DSM IV TR, from 1 January 2010 to 31 December 2012, hospitalized in Psychiatry Section III of Psychiatric Hospital "Dr. Gheorghe Preda" Sibiu, patients without somatic comorbidity (control group). For more accurate results, and evaluation of risk factors and evolution, we performed a statistical analysis of batch N1 depending on the etiology of liver disease, HVB=30 (chronic hepatitis B) and HCV=33 (chronic hepatitis C).

Statistical tools

Data processing was performed by Microsoft Excel with XLSTAT suite for MS Excel and secondary processing data was performed using Pivot Tables, Statistical Functions, Chart and Analysis of Data commands of Excel. Complex statistical tests (Chi square, Fisher exact, Student and ANOVA) were performed by XLSTAT module commands or using SPSS.

RESULTS

Study group N=121 was divided in order to achieve the research objectives into two subgroups: N1=63 patients with a diagnosis of major depressive episode or recurrent depressive disorder, previously diagnosed with chronic viral hepatitis (HBV=30 chronic hepatitis B and HCV=33 chronic hepatitis C) and N2=58 patients diagnosed with major depressive episode or recurrent depressive disorder without liver comorbidity.

Sociodemographic data obtained showed for our study group N=121 predominance of females (61.98%), significantly different from the sex distribution in the general population ($p<0.05$), the urban residential environment (76,86%) ($p<0.001$), professional education (49.59%) and maximum incidence of depressive disorder in the age group 50-59 years (62.81%). The association of depression with chronic viral hepatitis type B occurs particularly in younger patients (48.53 ± 10.39 years) ($p <0.05$).

The onset of major depressive disorder has been diagnosed in patients with subtype B infection diagnosis before or simultaneous with diagnosis of liver disease (56.66%) and after

diagnosis of chronic hepatitis type C (75.76%) (p<0 05) mainly in the age group 50-59 years (60.32%), with more than three episodes of disease recorded during the study (51.23%), number of episodes influenced by the presence of chronic hepatitis (p <0.001), especially subtype B. Severity of depressive symptoms was assessed by rating scales, the average scores being at the border between medium and severe depression (HAM-D 24.02±2.70, MADRS 25.90± 2,95) with a higher score for patients diagnosed only with depression (p<0.01).

The main psychiatric comorbidity were personality disorders (23.97%) more frequently in patients with chronic hepatitis B (30.00%) (p<0.05). The most common somatic comorbidities (35.54%) were essential hypertension, painful chronic ischemic heart disease and diabetes, predominantly in patients with chronic hepatitis.

Pharmacological therapy of depression was performed for the entire study group mainly with Selective Serotonin Reuptake Inhibitors (SSRIs) (52.89%), Selective Serotonin Reuptake of Serotonin and Norepinephrine (SNRI) (26.98%), and tianeptine (9.92%), while the combination of antipsychotics was performed only in patients who don't had a diagnosis of viral hepatitis (22.41%) (p <0.001).

The main pharmacological antiviral medication used in the treatment of chronic hepatitis was the interferon (20.63%), the largest share being registered in those who have been diagnosed with chronic hepatitis type C (11 patients) (p<0.05). Laboratory investigations (liver puncture and histopathology) were used in a number of 32 patients (50.79%) demonstrating the existence of a moderate hepatic impairment, especially in patients with hepatitis C.

Assessment of cognitive recorded average MMSE scores 27.48±2.26 (N1=63) and 29.24± 0.88 (N2=58), which emphasizes the vulnerability of cognitive status for patients with depressive disorder associated with viral liver infection. (p<0.0001)

DISCUSSION

The onset of psychiatric disorder was consecutive to liver infection (60.32%), thus bringing into question the role of the vulnerability manifested at both somatic and especially psychological level, both as a result of drug therapy antiviral and psychotrauma effects of liver disease severity and awareness of the effects that it has on the individual. The mean scores in the evaluation scales were high significantly correlated as in group N (p<0.0001), N1 (p<0.0001) and N2 (p<0.0001)

The number of hospitalizations (identical in the number of episodes of depressive illness) was a in highly significant direct correlation (p=0.001) with the severity of the

depression expressed by the HAM-D17 scores, both in N=121 group, where the patients with more than four episodes disease showing a severe depressive symptoms (HAM-D17 25.25±2.38), and N1=63 ($p<0.05$), being a strong argument to support that chronic viral hepatitis is a factor who predict the unfavorable of depressive disorder. We found similar results for assessing the severity of depressive disorder with MADRS scale ($p<0.05$).

SSRIs were the most commonly used class of antidepressant drugs, but the most important improvement in depressive symptoms, as measured by the HAM-D17 (22.25±1.06) and the MADRS (24,00±1.41) was obtained using tianeptine.

Cognitive impairment was present in the whole study group N=121 and was directly correlated with patient age ($r =-0.289$, $p<0.005$) and the presence of chronic liver infection (MMSE 27.48±2.26) ($p<0,0001$), highlighting the negative effect of these comorbidity.

CONCLUSIONS

1. The association between depressive disorder and chronic viral hepatitis was present in 63 patients (52.07%, N1 group), divided into hepatitis B – 30 (24.79%) and hepatitis C – 33 (27.27%), thus representing an important segment of psychiatric pathology treated in Psychiatry Section III of Psychiatric Hospital "Dr. Gheorghe Preda" Sibiu between 1 January 2010 – 31 December 2012. Patients with depressive disorder with comorbid liver had a share of 47.93% (N2).
2. Compared with the general population, socio-demographic risk factors identified for the development of depressive disorder for the entire group N was the urban areas (76.86%) ($p<0.001$) and female gender (61.98%) ($p<0,05$) without affecting in a significant way the association of depression with comorbid chronic viral hepatitis.
3. The occurrence and type of liver infection is affected in patients diagnosed with depression by their age (viral hepatitis type B – 48.53±10.39 years respectively viral hepatitis type C – 54.12±7.67 years) ($p<0.05$).
4. The evolution of depressive disorder measured by the number of hospitalizations ($p<0.001$), and the severity of the symptoms assessed on HAM-D and MADRS ($p<0.01$) were not influenced by the presence of chronic hepatitis, regardless of its etiology.
5. The large number of episodes of illness influenced highly statistically significant ($p=0.001$) the severity of depressive disorder expressed through scores on work tools for the entire study group N, being an independent risk factor for unfavorable development of depression, with or without comorbidity with viral chronic liver infection.

6. Personality disorder was identified as a significant psychiatric comorbidity in patients diagnosed with depressive disorder and chronic viral hepatitis type B ($p<0.05$).
7. Essential hypertension (34 patients), chronic ischemic painful (15 patients) and diabetes mellitus (5 patients) were the main somatic comorbidities significantly associated ($p <0.05$) with depression and chronic hepatitis (group N1).
8. SSRIs (52.89%), SNRIs (26.98%), and tianeptine (9.92%) were antidepressants used for the treatment of depression in whole group N, therapeutic decision was not not influenced by liver comorbidity (N1), while the combination of antipsychotics with antidepressant medication was influenced highly statistically significant ($p<0.001$) by hepatic comorbidity, being used only in patients with depressive disorder (N2).
9. Among the antidepressants used, tianeptine has led to the best results in improving depressive symptoms, in patients with depression (HAM-D17, 22.25 ± 1.06, $p<0.05$, MADRS, 24.00 ± 1, 41, $p <0.05$) and those associated with chronic hepatitis (HAM-D17, 22.1 ± 1.17, $p <0.05$ MADRS, 24.00 ± 1.66, $p<0.05$).
10. Antiviral therapy with interferon was present in 13 patients (20.63%), the majority (11 patients) were infected with type C ($p<0.05$).
11. Assessment of cognitive status indicates the tendency to cognitive impariment (MMSE – 28.32 ± 1.95), more pronounced in patients with chronic hepatitis associated with depressive disorder (27.48 ± 2.26), especially in those with hepatitis C (27.30 ± 1.93) ($p<0.0001$).
12. Cognitive impairment was highly significant associated with age of patients in both N2 ($p<0.005$), and N1 ($p<0.001$) study groups.
13. Clinical peculiarities in patients with major depressive disorder and chronic hepatitis revealed by our study were the comorbid personality disorders and risk for somatic comorbidities (cardiovascular diseases or diabetes mellitus).
14. Evolutionary peculiarities in patients with major depressive disorder and chronic hepatitis are the emergence of cognitive impairment and favorable therapeutic response to tianeptine and risks were age over 48 years, therapy with SSRIs and SNRIs, type C virus liver infection, antiviral therapy with interferon, damage of liver structures and function as evidenced by liver puncture, predominantly A2F2 degree.
15. We believe that there are arguments for a differentiated therapeutic approach in patients with major depressive disorder and chronic hepatitis associated with constant monitoring of cognitive impairment and liver function, including liver puncture, and metabolic and cardiovascular risk.

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