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Alexithymia, Suicide Ideation and Homocysteine Levels in Drug Naïve Patients with Major Depression: A Study in the "Real World" Clinical Practice

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Objective: This study was performed to elucidate relationships between alexithymia, suicide ideation and homocysteine levels in drug-naïve outpatients with major depressive disorder (MDD).
Methods: Sixty seven outpatients with MDD with melancholic features were evaluated by the means of the Hamilton Depression Rating Scale, the Toronto Alexithymia Scale (TAS-20), the Scale of Suicide Ideation, and homocysteine levels.
Results: Alexithymic subjects showed higher scores on all scales and higher homocysteine levels. Regression analysis shown higher homocysteine levels and TAS-20' "Difficulty in Describing Feelings" dimension, in turn being associated with higher suicide ideation.
Conclusion: In conclusion, alexithymic MDD outpatients may characterize for homocysteine dysregulation that may be linked to suicide ideation, regardless depression' severity. However, study limitations are discussed and must be considered.

KEY WORDS: Affective symptoms; Alexithymia; Depression; Suicidal ideation; Homocysteine.

INTRODUCTION

Major depressive disorder (MDD) is one of the most disabling and common psychiatric disorders worldwide.[1)] The relationship between MDD and alexithymia has been investigated in several studies.[2,3)] Whenever associated, alexithymia is a risk factor for MDD itself, and/or a relatively stable personality trait further increasing the overall burden.[4)]

Homocysteine levels have been extensively investigated in MDD cases, especially in the elderly.[5,6)] Higher homocysteine levels are often observed in course of MDD vs. control subjects and may represent a risk factor for poorer memory function and global cognitive performance, regardless depression severity.[6)] However, to date, no studies have specifically assessed the relationships between alexithymia, suicide ideation and homocysteine

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levels.

To the best of our knowledge, this is the first study aiming at: i) testing whether any differential profile in homocysteine levels and suicidal ideation in MDD patients would depend on concurrent presence of alexithymia or not; ii) assessing the impact of selected clinical variables in the prediction of suicidal ideation using a blockwise linear regression analysis.

METHODS

A total of 67 adult outpatients (34 males, 33 females) with a Diagnostic and Statistical Manual for Mental Disorders, 4th edition, text revision (DSM-IV-TR)[7] diagnosis of MDD with melancholic features were recruited at several mental health facilities across Central Italy in an everyday clinical practice setting. All diagnoses were made by psychiatrists with at least 5 years clinical experience and confirmed with the Structured Clinical Interview for DSM-IV (SCID).[8] Eligible patients met the criteria for a major depressive episode (MDE) with a score ≥16 at the Hamilton Depression Rating Scale (HAM-D), 17-item version.[9] Patients' age ranged between 18 to 45 years, being naïve treatment seeker for MDE. Within subjects diagnosed with MDD we distinguished between patients with their first depressive episode (n=47, 70.1%) and patients with recurrent depressive episodes with one depressive episode before the present one (n=20, 29.9%), but never treated with antidepressants or other psychotropics. Thriry-nine patients (58.2%) were smokers.

Patients receiving psychotherapy treatment were excluded. Additional exclusion criteria were the following; concurrent treatment with vitamin B supplements, any additional axis-I disorder, including substance use disorder, mental retardation or presence of any organic mental disorders.

Alexithymia was evaluated by the means of the Italian version[10] of the 20-item Toronto Alexithymia Scale (TAS-20); a TAS-20 score ≥61 was considered indicative of alexithymia.[11] The TAS-20 has a three-factor structure: Factor I assesses the ability to identify feelings and to distinguish between the feelings and bodily sensations of emotional arousal (difficulty in identifying feelings, DIF); Factor 2 reflects the inability to communicate feelings to other people (difficulty in describing feelings, DDF); Factor 3 assesses externally-oriented thinking (EOT).

In order to assess suicidal ideation, the total score of the clinician-rated Scale of Suicide Ideation (SSI) was administered.[12] MDD severity was assessed with the 17-item HAM-D total score.[9]

Weight was measured (in light indoor clothing with shoes removed) using a balance beam scale, and height was measured using a stadiometer. Weight and height were used to calculate body mass index (BMI) expressed as kg/m^2. The mean BMI was 22.1±1.7 kg/m^2.

Serum homocysteine was measured collecting venous blood samples. Blood was drawn into tubes containing ethylenediaminetetraacetic acid/K3, placed on ice immediately thereafter, and centrifuged at 4°C. Plasma was separated and immediately stored at −80°C before it was analysed. Blood samples were collected between 7:00 am and 8:30 am, after the patient had fasted for at least 10 hours.

The rating scales' records and homocysteine measurements were collected as a part of everyday "real world", routine clinical practice evaluation and assessment of patients. However, each patient had to understand the nature of the study and signed a valid informed consent document prior to enrolment. A waiver was granted from institutional ethical committee as this was a retrospective study.

Statistical Analysis

The differences between individuals with and without alexithymia were tested using analyses of covariance (ANCOVA) with TAS-20 positivity/negativity as a factor and age, gender, smoking status, duration of illness, and recurrence and BMI scores as covariates. Cohen's d effects sizes were likewise calculated. A block-wise linear regression analyses were performed to ascertain which variables were associated with the severity of suicidal ideation (SSI as dependent variable). Age, gender, smoking status, duration of illness, recurrence, BMI and HAM-D scores were added to the first block. At the second block, homocysteine levels were added to the model. The DIF, DDF, and EOT subscales of the TAS-20 were entered in the third, and last step. The p values ≤0.05 were deemed statistically significant. All statistical testing was two-tailed. Statistical analyses were performed using SPSS for Windows release ver. 10 (SPSS Inc., Chicago, IL, USA).

Table 1. Results of the linear regression analysis with SSI as dependent variable and other variables as independent

	Unstandardized coefficients		Standardized coefficient	t	*p* value	95% CI for *B*
	B	SE	Beta			
Homocysteine levels	0.39	0.08	0.42	4.01	<0.001	0.16-0.46
DDF	0.38	0.05	0.44	3.21	0.006	0.07-0.28

Only statistically significant variables are shown.
SSI, Scale of Suicide Ideation; SE, standard error; 95% CI, 95% confidence interval; DDF, difficulty in describing feeling.
R^2=0.64, dF=55, F=9.98, $p<0.001$.

RESULTS

Sex comparisons between all demographic and clinical variables showed no significant differences concerning any of the accounted variables. The mean duration of illness was 15.3±6.4 months. The total score for the TAS-20 in the whole sample was 50.3±13.8. Twenty-five (37.3%) patients had a total score ≥61 at the TAS-20, thus being recorded as alexithymic subjects.

Comparison between individuals with or without alexithymia upon controlling for age, gender, smoking status, duration of illness, recurrence and BMI, showed that alexithymic subjects had greater severity of MDD according to the HAM-D (28.4±4.2 vs. 23.5±3.1, degree of freedom [dF]=1, 67 F=37.8 $p<0.001$, Cohen's d=1.33), higher homocysteine levels (15.9±4.5 vs. 12.0±3.2 μmol/L, dF=1, 67 F=25.4 p=0.006, Cohen's d=1.00) and higher SSI scores (7.1±2.2 vs. 2.0±2.0, dF=1, 67 F=94.7 $p<$ 0.001, Cohen's d=2.43) compared to non-alexithymic cases. Effect size calculation showed that the magnitude of the group effect between alexithymics and non-alexithymics concerning these three variables was large.

In the linear regression models (Table 1) higher homocysteine levels and DDF dimensions of TAS-20 were associated with higher suicide ideation (using SSI as dependent variable). In the current analyses, the R^2 values accounted for 64% of variance in the SSI score. In addition, Durbin-Watson coefficient was 2.004 (near to the optimum of 2.0). A scatter plot of residuals and a plot of regression-standardized residuals indicated a near normal distribution.

DISCUSSION

To our knowledge, this was the first study that evaluated the relationships between alexithymia, homocysteine levels and suicide ideation in a sample of outpatients with MDD.

Patients with alexithymia showed increased MDD severity, higher homocysteine levels and more severe suicide ideation and these results may be explained according to the Freyberger's concept of acute "secondary alexithymia" as a reaction to stressful situations.[13] Acute secondary alexithymia may be explained as a transitory, state-dependent phenomenon that results as an effect of personal distress, and which may decrease once an acute disease episode has resolved. In fact, our results may reflect a state-dependent phenomenon, perhaps related to higher MDD severity. Interestingly, we found that DDF dimension of TAS-20 was associated with higher suicide levels in patients with MDD and this is in line with the findings of a previous study.[14] Moreover, these results may be also in accordance with the stress-alexithymia hypothesis[15]: patients with alexithymic traits may be suffering from chronic stress reaction that could itself promote persistent and often subclinical increases in inflammatory and oxidative factors such as C-reactive protein, serum lipid dysregulation and homocysteine.

According to Folstein *et al.*,[16] high levels of homocysteine would be associated with cerebrovascular disease, monoamine neurotransmitters, and depression of mood itself. According to the later hypothesis, homocysteine levels may cause cerebral vascular disease and neurotransmitter deficiency, which would on turn cause depression of mood and suicide ideation. However, all considered, the results of our study support the notion that depressed alexithymics with DDF may have a homocysteine dysregulation that may be linked in a unclear way to suicide risk. Therefore, we recommend to screen depressed patients for both alexithymia and suicide ideation (as all authors do in their everyday clinical practice), regardless of depression severity, and to evaluate also homocysteine in order to have a further indirect potential biomarker for suicide risk. One can argue that treating hy-

perhomocysteinemia would reduce suicide risk; however, to date, no studies are present confirming this hypothesis even if oxidative stress may play a role in depression severity thus increasing suicide risk.[17,18]

To date, it is unclear how hyperhomocysteinemia may contribute to the development and maintenance of psychiatric disorders, alexithymia and suicide ideation, but some studies tried to unravel this issue.[19-22] It has been suggested that elevated levels of homocysteine may compromise blood-brain barrier integrity probably increasing its permeability through glutamatergic NMDA receptor-dependent regulation of adherens and tight junctions.[23,24] Therefore, hyperhomocysteinemia may cause a direct damage to the neurons causing psychiatric disoders through several mechanisms that may be interconnected[25,26]: 1) straight neuronal toxicity through specific receptors on the neurons, inducing cell death, 2) impairing the cerebral vascularization and, particularly, the endothelium of small brain vessels. This may cause neuronal death indirectly also impairing the neurotransmission which is involved in the basic functions of the brain, consequently modifying the regular functioning of the mind of a subject.[27] Furthermore, a fault in methylation processes is thought to be essential to the psychiatric manifestations due to the lack of vitamins B6, B12, and folate.[28] All these vitamins are closely connected with homocysteine metabolism such that total serum hyperhomocysteine level is considered to be a sensitive and important marker of the functional brain deficit of such vitamins.[29,30] Last but not least, as methionine is the precursor of S-adenosylmethionine, which is the direct methyl donor in several reactions involved in the biosynthesis of the monoaminergic neurotransmitters,[31-33] the altered metabolism of homocysteine and, therefore, the presence of a condition of hyperhomocysteinemia may cause an impairment in the levels of monoamine neurotransmitters causing mood disturbance and suicidal ideation.[34] All considered, as the results of our study pointed out that in alexithymic subjects with MDD we found an higher level of homocysteine that was correlated to increased suicide ideation, it can be hypothesized that changes of peripheral blood homocysteine levels may affect brain activity and induce suicidal ideation and alexithymia, but further studies are needed.

The present study was exploratory in nature. As such, we would prompt the following limitations in the interpretation of the preliminary results. The first limitation was the relatively small sample size (even if all the evaluated patients were drug naïve). Moreover, even if severity of MDD and suicidal ideation were analysed using clinician-rated rating scales, alexithymia was assessed by a self-rated scale, with possible biases due to the inherent nature of self-rating scales. Furthermore, we employed a cross-sectional design that limits statements regarding causality: our study lacks follow-up data. In fact, the cross-sectional nature of the present study precluded any firm conclusion about any eventual hierarchical role interaction of either alexithymia or hyperomocysteinemia. Finally, in the present study we did not evaluated serum folate levels that may give more meaningful results: future studies should be take into account this point.

Therefore, prospective studies are needed, with repeated-measure design of serum homocysteine prior, during and after the acute pharmacological treatment.

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