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Regular Article

Mood symptoms and serum lipids in acute phase of bipolar disorder in Taiwan

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Abstract Serum lipids have been found to play important roles in the pathophysiology of mood disorders. The aim of the present study was therefore to investigate the relationship between symptom dimensions and serum cholesterol and triglyceride levels, and to explore correlates of lipid levels during acute mood episodes of bipolar I disorder in Taiwan. Measurements were taken of the serum cholesterol and triglyceride levels in patients with bipolar I disorder hospitalized for acute mood episodes (68 manic, eight depressive, and six mixed). The relationships between serum lipids levels and various clinical variables were examined. The mean serum levels of cholesterol (4.54 mmol/L) and triglycerides (1.16 mmol/L) of sampled patients were comparable to those of the general population in the same age segment. Severe depressive symptoms and comorbid atopic diseases were associated with higher serum cholesterol levels. A negative association was noted between serum triglyceride levels and overall psychiatric symptoms. Compared with previous studies on Western populations, racial differences may exist in lipids profiles of bipolar disorder patients during acute mood episodes. Increased serum cholesterol levels may have greater relevance to immunomodulatory system and depressive symptoms, in comparison with manic symptoms.

Key words atopic disease, bipolar disorder, cholesterol, depression, triglycerides.

INTRODUCTION

Substantial evidence suggests that serum lipid levels may be correlated with variations in mental state.[1] Prior studies linked low cholesterol activity with both suicidal tendencies[2,3] and depressive symptoms.[4,5]

With regards to bipolar disorders, low cholesterol levels have been reported in manic episodes,[6,7] mixed episodes[8,9] and remitted states.[7,10] There are a variety of factors influencing serum lipid levels in patients with bipolar disorders, including gender, age, body mass index (BMI), alcohol use, medication, diet, comorbid physical illness, symptomatic severity, and the subtype of mood episode.[8,9] However, there is a distinct paucity of data on the relationships between clinical characteristics and serum lipid profiles in bipolar disorders. Conclusions drawn by the few published studies on the severity of symptoms and serum lipid levels in bipolar disorder in this area are inconsistent.[4,7,10] In consideration of overlapping clinical manifestations among the subtypes of mood episode in the broad area of bipolar spectrum,[11] it is worthwhile to evaluate the effect of mood symptom dimensions, rather than mood episode categories, on blood lipid metabolism.

We hypothesize that serum lipids of bipolar disorder patients during acute mood episodes may be altered by certain mood symptoms. The present study aims to investigate the relationships between mood symptom dimensions and serum cholesterol and triglyceride levels, and to explore correlates of lipid levels during acute mood episodes of bipolar I disorder.

METHOD

Subjects

All of the subjects for the present study were drawn from Taipei Medical University Hospital and Taipei

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City Psychiatric Center, a psychiatric teaching hospital providing comprehensive psychiatric services and assigned as a center for the northern Taiwan catchment area. Guidelines for treatment decisions in bipolar disorder had previously been provided at the hospital.

Acute inpatients meeting the DSM-IV diagnostic criteria for bipolar I disorder, manic episode, mixed episode, or major depressive episode, and who were aged between 16 and 45 years, were invited to participate in the present study between 1996 and 2004. After being provided with complete detailed information on the overall purpose of the study, those subjects wishing to participate were subsequently asked to provide written informed consent.

The subjects were then diagnosed and rated by two experienced psychiatrists using the well-validated semi-structured schedule for Taiwanese psychiatrists, the Psychiatrist Diagnostic Assessment (PDA),[12] which has been successfully used in prior bipolar disorder studies and has been extensively described elsewhere.[13,14] Through an evaluation of the available clinical data and all other available information, including a review of the subjects' medical records and the confirmation of their family members, we were able to obtain accurate diagnoses on all of the patients. Those patients with comorbid substance use disorders (including alcohol-related disorders), pregnancy, any prior history of hyperlipidemia, or any other active medical diseases, were excluded from the study, as were those who, in the 2-week period prior to the study, had used any medication known to affect blood lipids (phenytoin, phenobarbital, steroids, thyroid supplementation, oral contraceptives, thiazide diuretics, statin-class medications).

Variables

The well-recognized historical clinical features of the illness were collected for analysis, with the continuous variables adopted for the present study including current age, age at onset, years of illness, daily dosage of antipsychotics and mood stabilizers, number of prior episodes, Young Mania Rating Scale (YMRS) scores,[15] Hamilton Depression Rating Scale (HDRS) scores[16] and the Brief Psychiatric Rating Scale (BPRS) scores.[17] The categorical variables included smoking habit, coexisting psychotic features, compliance, family history (among first-degree relatives), depressive syndrome (HDRS ≥ 8),[18] manic syndrome (YMRS ≥ 13),[13] prior depressive episodes, and comorbid atopic disease.

Assays

Serum lipid levels, including total cholesterol and triglyceride levels, were measured in the laboratory at Taipei Medical University Hospital by enzymatic determination (cholesterol oxidase phenol 4-aminoantipyrine peroxidase [CHOD/PAP], Boehringer Mannheim, Mannheim, Germany).[19,20] Blood samples were taken from the antecubital vein between 08.30 and 09.30 hours, after the patients had fasted for at least 8 h.

Statistical analysis

Student *t*-tests were conducted in order to compare the respective serum cholesterol and triglyceride levels, with each of the categorical clinical features as the independent variable. Pearson product–moment correlations were used in order to assess any association between the continuous clinical variables and both serum cholesterol and triglyceride levels. Two-tailed $P < 0.05$ was considered to be significant.

RESULTS

A total of 82 patients with bipolar I disorder (37 male, 45 female) were recruited during acute mood episodes, with a mean age of 34.7 ± 11.9 years, including 68 patients suffering from manic episode, six patients suffering from mixed episode and eight patients suffering from depressive episode.

In terms of their medication status, at the time of the index episode, 45 patients had been drug free for at least 6 months, and seven patients had been medicated with only antipsychotic drugs. During admission, medications were prescribed according to clinical status and treatment guidelines. At the time of their entry into the study, 74 patients had taken at least one mood stabilizer, including lithium ($n = 27$), valproic acid ($n = 24$), carbamazepine ($n = 3$), lithium plus valproic acid ($n = 16$) and lithium plus carbamazepine ($n = 4$). No patients had received medication consisting of any combinations of valproic acid and carbamazepine, or lithium, valproic acid and carbamazepine; but 54 patients were treated with a combination of typical antipsychotic and mood stabilizer drugs, a further eight patients were treated with atypical antipsychotic drugs and mood stabilizers, and four patients were treated with a combination of a mood stabilizer and an antidepressant. When blood samples were obtained during acute phase, 50 patients (61.1%) had taken medication for <24 h, 19 patients (23.2%) for 1–7 days, and 13 patients (15.7%) for >7 days. The mean length of medication at the time of sampling blood was 8.9 ± 26.0 days. Although 10 patients had a past history of atopic disease, they had not taken any medication for this at the measurement of blood lipid.

Table 1. Continuous variables regarding clinical features for bipolar patients ($n = 82$) in acute phase

Continuous variables	Mean	SD
Current age (years)	34.7	11.9
Age at onset (years)	23.5	8.1
Length of illness (years)	11.3	6.3
Body mass index (kg/m^2)	24.2	5.2
No. prior episodes	5.8	4.1
Daily dosage of lithium ($n = 45$) (mg)	882.2	210.3
Daily dosage of carbamazepine ($n = 7$) (mg)	685.7	195.2
Daily dosage of valproic acid ($n = 37$) (mg)	1044.6	266.6
Daily dosage of mg chlorpromazine equivalent ($n = 65$)	314.8	224.4
YMRS scores	30.1	11.9
HDRS scores	4.7	10.6
BPRS scores	16.8	13.3
Serum cholesterol level (mmol/L)	4.54	0.87
Serum triglyceride level (mmol/L)	1.16	0.82

BPRS, Brief Psychiatric Rating Scale; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

Table 2. Dichotomous variables for acute bipolar patients ($n = 82$)

	Cholesterol (mmol/L)		Triglycerides (mmol/L)	
Variables	Mean	SD	Mean	SD
Gender				
Male ($n = 37$)	4.36	0.90	1.37	1.84
Female ($n = 45$)	4.69	0.84	1.23	1.01
Smoking habits				
Yes ($n = 21$)	4.54	0.82	1.37	1.02
No ($n = 61$)	4.54	0.90	1.26	1.56
Psychotic features in the index episode				
Yes ($n = 58$)	4.57	0.88	1.14	0.80
No ($n = 24$)	4.48	0.88	1.59	2.19
Positive family history of mood disorder in first-degree relatives				
Yes ($n = 20$)	4.78	0.84	1.89	2.51
No ($n = 62$)	4.46	0.88	1.10	0.78
Prior depressive episodes				
Yes ($n = 25$)	4.31	0.65[†]	1.38	2.20
No ($n = 57$)	4.67	0.93	1.26	0.92
Comorbid atopic disease				
Yes ($n = 10$)	5.17	0.75[‡]	1.40	1.22
No ($n = 72$)	4.51	0.86	1.29	1.54
HDRS ≥ 8				
Yes ($n = 15$)	4.94	0.80[§]	1.33	1.04
No ($n = 67$)	4.45	0.88	1.13	0.77
YMRS ≥ 13				
Yes ($n = 70$)	4.88	0.77	1.29	1.52
No ($n = 12$)	4.53	0.87	1.32	0.97

[†] $t = 1.765$, $P = 0.081$; [‡] $t = 2.283$, $P = 0.025$; [§] $t = 2.014$, $P = 0.047$.

HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

The continuous variables of sampled patients, by clinical characteristics, are presented in Table 1.

The serum cholesterol and triglyceride levels of sampled patients, by clinical characteristics, with the various categorical variables, are presented in Table 2.

The patients with atopic diseases and depressive syndrome (HDRS ≥ 8) had significantly higher mean serum cholesterol levels. The 15 patients with depressive syndrome (HDRS ≥ 8) included eight depressive, six mixed patients, and one patient with depressive syndrome without meeting the criteria of depressive or mixed episode. The serum cholesterol levels of 21 manic patients and four depressed patients with prior depressive episode were lower than those of patients without prior depressive episodes, with marginal statistical significance ($P = 0.081$).

Of the continuous variables, the symptomatic severity of mania (YMRS scores) did not demonstrate significant correlation with serum cholesterol levels ($r = -0.131$, $P = 0.268$) or triglyceride levels ($r = -0.122$, $P = 0.304$), but the symptomatic severity of depression (HDRS scores) had a marginally significant correlation with serum cholesterol levels ($r = 0.204$, $P = 0.065$) as did age ($r = 0.200$, $P = 0.09$). Serum triglyceride levels were found to have a significantly negative correlation with BPRS, as shown in Fig. 1 ($r = -0.251$, $P = 0.031$), and two subscales of the BPRS (thinking disturbance, $r = -0.318$, $P = 0.007$; hostile/suspiciousness, $r = -0.393$, $P = 0.001$). Moreover, there was no significant difference in mean serum level of cholesterol or triglyceride among patients with manic, mixed, or depressive episode (cholesterol, $F = 2.227$, $P = 0.115$; triglyceride, $F = 0.135$, $P = 0,874$, respectively). Finally, analysis concerning correlation between serum lipids and symptom scores among patients with manic and mixed episodes did not show statistic significance (data not shown).

DISCUSSION

The present study demonstrates a positive correlation between serum cholesterol levels and the severity of depression during acute mood episodes of bipolar I disorder. However, regardless of current subtype of mood episode, patients with prior depressive episodes tended to have lower serum cholesterol levels. Our

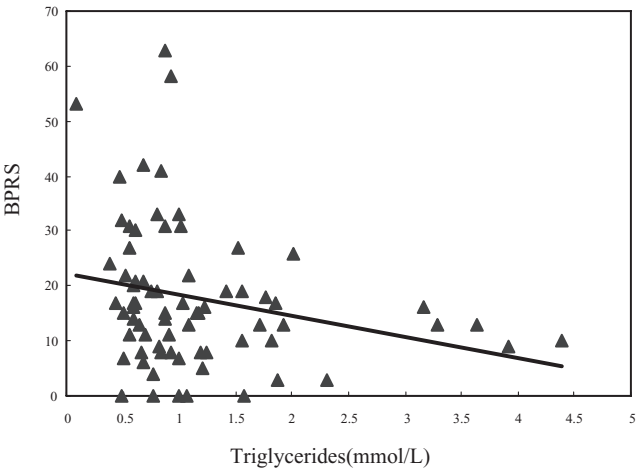

Figure 1. Relationship between serum triglyceride levels and Brief Psychiatric Rating Scale (BPRS) scores in acute bipolar I patients ($r = –0.251$, $P = 0.031$).

findings suggest that, for bipolar disorder patients experiencing acute mood episodes, depressive symptoms seem to play a role in upregulating the circulatory cholesterol regardless of various mood polarities. This finding is in line with the extant reports on the Western populations.[8,9] Most items on HDRS[18] are scaled so that increasing scores represent increasing severity, and all the items are designed to measure the severity of depressive symptoms. It is less clear whether different scores on certain items actually assess the same underlying construct/syndrome.[21]

Our early work found a state-dependent alternation of inflammatory response system in bipolar manic patients.[13] The findings of high serum cholesterol levels in patients with more severe symptoms, and low levels in those with prior depressive episodes are postulated to be related to the difference of trait effect and state effect of cholesterol regulation on mood symptoms. Serum cholesterol may change serotonin neuronal activity by altering presynaptic re-uptake and post-synaptic receptor numbers or function,[8] and it may have a state effect on patients in the acute phase, which was stronger than the trait effect on patients with prior depressive episodes. It also supports the concept that unipolar mania may be a separate status.[22] However, the hypothesis will need to be evaluated in future studies.

Several partly overlapping definitions of bipolar spectrum disorder have been proposed and broadly discussed, including mixed depression or dysphoric mania.[11] Full syndromal intertwining of depressive and manic states into dysphoric or mixed mania (as emphasized in DSM-IV) is relatively uncommon. Unlike some of the earlier studies, which undertook their comparisons in terms of various mood disorders or mood episodes,[4,8,9] the present results are strengthened by an increased level of sensitivity in order to detect correlations between lipid profiles and mood symptoms, particularly when the severity of the symptoms was below a particular mood episode threshold. Moreover, because the present bipolar patients with atopic diseases were found to have higher serum cholesterol levels, this may provide additional evidence to support alternation of the immunomodulatory system involving the metabolism of circulatory lipids.[23,24]

The mean serum levels of cholesterol (4.54 mmol/L) and triglycerides (1.16 mmol/L) for sampled patients were comparable to those of the general population in the same age segment estimated from a representative national sample.[25] Nonetheless, they are obviously lower than those reported for Western populations (>4.76 mmol/L) as well as those for Western patients with mood disorders.[8,9,26] Hence, the fact that the lipid profiles of bipolar patients do vary across ethnic groups should be emphasized before attempting to carry out any international comparison.

The triglycerides, which are not regarded as a major biochemical part of the brain structure, seems less important than cholesterol; but patients with mood disorder, including depressive, bipolar and schizoaffective disorders, have been found to have elevated triglyceride levels.[4] Originally the BPRS was not designed to identify independent dimensions of psychopathology but to assess the overall psychiatric symptoms in psychotic patients, although subscales of BPRS also have descriptive utility.[17] In the present study, serum triglyceride levels were lower in bipolar disorder patients with greater severity of overall psychiatric symptoms on the BPRS, particularly in subscales of thinking disturbance and hostile/suspiciousness, but they were not found to have any direct association with either manic or depressive symptoms. In further studies, Positive and Negative Syndrome Scale (PANSS) should be used to evaluate the effect of psychotic symptoms on serum lipid level. The different presentation of serum lipids reinforces the argument that cholesterol and triglycerides may play distinct roles in the pathophysiology of bipolar disorder.

Some methodological limitations should be addressed, which will lead to careful interpretation of the present data. First, the present subjects consisted of more manic patients and only approximately 30% of patients ($n = 25$) had prior depressive episodes. These phenomena can be explained by Berkson's bias, in that bipolar patients with prior depressive episodes may have more recurrent depressive episodes,[27] which usually do not result in indication for acute admission, but recurrent mania patients tend to be hospitalized for disturbing behavior or hyperactivity. This is also found

in another study in Taiwan.[28] Hence, conclusions should be drawn with some caution. Second, we did not obtain serum lipid levels during subsequent remission; therefore, further studies examining more time points are necessary in order to determine any alternation in the severity of the lipid profile within the same group. Third, although only a few patients took atypical antipsychotic agents, and no correlation was found between the daily dosages of medication and each serum lipid level, the influence of psychotropic medication, particularly atypical antipsychotics, on serum lipid levels cannot be entirely excluded. Fourth, we did not evaluate certain factors that could affect serum lipid levels, such as dietary intake, nutritional status, fractionated cholesterol subtypes or physical activity; but given that the acute inpatients in the present study received hospital standard meals during the index hospitalization, this may have reduced such individual variation.

In conclusion we have found that serum cholesterol levels are more relevant to depressive symptoms than manic symptoms, and that the role of cholesterol and triglycerides in the pathophysiology of bipolar disorder may vary during acute mood episodes. Also, racial differences may exist in lipid profiles of bipolar disorder between Western and Eastern patients. The fact that comorbid immunity-related diseases, such as atopic disease, may elevate serum cholesterol levels indicates the need for further studies with a particular focus on the immunomodulatory mechanism and lipid metabolism.

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