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ORIGINAL PAPER

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Hypocholesterolemia during mixed manic episodes

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Abstract *Background* An association of relatively low serum cholesterol with both depression and suicide has been reported. Depressive symptoms, including suicidality, are defining features of mixed mania. Few studies have considered differences in cholesterol levels in subjects during mixed bipolar episodes. *Methods* Fasting serum cholesterol levels obtained from 174 subjects evaluated during mixed and pure manic episodes were compared using ANOVA statistics. Sex was included in the analysis and age was used as a covariate. Cholesterol levels in the total manic cohort and in the mixed and pure manic subgroups were compared with national norms. *Results* Fasting serum cholesterol levels were lower in the mixed manic subtype compared to the pure manic subtype. As expected, cholesterol levels increased with age. No differences were noted between males and females. Cholesterol levels were lower in both the mixed and pure manic subtypes when compared with national norms. *Conclusion* Fasting serum cholesterol levels are low in manic patients, especially during mixed bipolar episodes. Cholesterol, which has been reported to be a negative acute phase reactant, may be lower during mixed states as a result of an immune activation.

Key words cholesterol · bipolar disorder · mixed manic states · acute phase response · suicide

Introduction

Mixed mania is an important bipolar episode subtype. Recent studies of the distribution of dysphoric mood symptoms during mania (Cassidy et al. 1998a) demonstrate that mixed mania is a distinct state, consistent with the view adopted by DSM-III, -IIIR and IV. In addition to sharing common depressive symptom profiles with major depression, mixed manic episodes have also been characterized by a female predominance, in contrast to a near equal sex distribution in manic episodes (Cassidy and Carroll, 2001a). Likewise, rates of neuroendocrine disturbances such as escape from dexamethasone suppression are higher during mixed manic episodes, similar to what is observed during depression (reviewed in Cassidy et al. 1998b). A paucity of African Americans (Cassidy and Carroll, 2001a), hypoalbuminemia (Cassidy et al., 2002) leukocytosis (Cassidy et al., 2002), and a late summer/fall seasonal peak (Cassidy and Carroll 2002) also appear common to both depression and mixed mania.

Two lines of evidence suggest a possible link between depression and serum cholesterol levels. First, increased rates of violent death including suicide (Muldoon et al. 1990) and the association of depressive symptomatology (Ernst et al. 1994, Ketterer et al. 1994) have been noted in subjects placed on low cholesterol diets or treated with statin-class medications. Second, higher rates of depression in subjects with hypocholesterolemia (Morgan et al. 1993, Rozzini et al. 1996, Steegmans et al. 2000) and lower cholesterol levels in depressed subjects (Cadeddu et al. 1995, Partonen et al. 1999) and subjects with affective disorders (Glueck et al. 1994) than in controls have been reported. Lower cholesterol levels have also been noted in suicidal subjects (Modai et al. 1994, Sullivan et al. 1994, Golier et al. 1995, Kunugi et al. 1997, Partonen et al. 1999, Sarchiapone et al. 2000) and hypocholesterolemia has also been implicated as a positive risk factor for suicide (Neaton et al. 1992, Papassotiropoulos et al. 1999), suggesting a possible association of hypocholesterolemia and syndromes characterized by elevated rates of suicide such as depression and mixed mania.

Few studies have addressed cholesterol levels during manic bipolar episodes. Swartz (1990) reported lower levels in hospitalized manic patients than in non-psychiatric controls, although others found no difference

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(Brandrup and Randrup 1967, Brown et al. 1992). In the only previous study of cholesterol levels during mixed manic episodes, Ghaemi et al. (2000) reported higher cholesterol levels in a group of 5 bipolar patients during mixed mania compared with 9 patients during manic episodes.

Similarities between mixed mania and major depression including symptom presentation, natural history and biomarkers, as well as associations of suicidality common to both, suggest that cholesterol levels might be lower in mixed manic episodes, similar to depression as well. The question is particularly germane to the clinical population in light of reports of possible associations between hypocholesterolemia and suicidality. In the current report we address two questions: First, whether fasting serum cholesterol levels collected during mixed bipolar episodes are lower than those collected during pure manic episodes. Second, whether fasting cholesterol levels during manic and mixed bipolar episodes differ from population norms.

Methods

Charts of patients admitted to John Umstead Hospital for the treatment of manic or mixed bipolar episodes between June 1992 and December 2000 were reviewed with IRB approval and admission cholesterol levels were identified. All patients met DSM-IIIR criteria for Bipolar Disorder, manic or mixed. Samples from patients having received carbamazepine, phenytoin or phenobarbital (Reddy 1985, Brown et al. 1992), steroids (Stern et al. 1973), thyroid supplementation (Greene et al. 1961), oral contraceptives (Wallace et al. 1979), thiazide diurectics (Grimm et al. 1981, McKenney et al. 1986) or statin-class medications within two weeks of blood sampling were excluded because of potential effects on total serum cholesterol levels, as were levels from subjects who were actively abusing alcohol (Allen and Adena 1985). Samples from patients diagnosed with concurrent active medical illness associated with disturbances in total cholesterol levels, such as liver dysfunction, thyroid disease (Abrams and Grundy 1981), immune disorders (Ettinger and Harris 1993) or active infections (Sammalkorpi et al. 1988) were excluded, as were non-fasting samples.

An ANOVA was conducted to compare cholesterol levels in the mixed and pure groups. Episode subtype was categorized as mixed employing a receiver operating characteristic (ROC) definition that requires two or more of five depressive symptoms (Cassidy et al. 2000). That definition is both more inclusive than the DSM definitions for Bipolar Disorder, mixed, (Cassidy et al. 2000, Cassidy and Carroll 2001b) and excludes symptoms that are nonspecific in the context of mania such as psychomotor agitation (Cassidy et al. 1997). Sex was included in the analysis because of potentially higher cholesterol levels in females (McPherson et al. 1978). Cholesterol levels also increase with age (McPherson et al. 1978), which was, therefore, included as a covariate.

In a secondary analysis, cholesterol levels were compared with national percentile norms established by sex and decade of age in the National Health and Nutrition Examination Surveys III (National Center for Health Statistics, 1994), and each subject categorized into one of 10 percentile-based groups established in the comparison study. These percentile groups were established at cutoff values for the 5^{th}, 10^{th}, 15^{th}, 25^{th}, 50^{th}, 75^{th}, 85^{th}, 90^{th}, and 95^{th} percentiles. A goodness of fit chi square was then conducted comparing the expected distribution with the actual percentile distribution for the overall cohort as well as for the pure and mixed subtypes. In an additional analysis the overall distribution of percentile assignments was inspected and chi square statistics computed comparing the subgroup of cholesterol levels in the lowest 10^{th} percentiles and the highest 90^{th} percentiles by manic subtype (mixed vs. pure).

Results

Serum cholesterol levels were identified for 386 patients collected during manic or mixed bipolar episodes. Forty-five samples were excluded, because they were not fasting levels. Twenty-six samples which were obtained from patients who had one or more concurrent medical condition that might affect cholesterol levels were excluded. These were positive HIV status (n = 6), hepatitis (n = 6), sarcoid (n = 2), systemic lupus erythematosus (n = 3), myositis (n = 1), cirrhosis (n = 2), hepatocellular degeneration (n = 1), acute infectious disease (n = 5), glomerular nephritis (n = 1), pregnancy (n = 1), cancer (n = 1) and thyroid disease (n = 44). In addition samples from 111 patients who had been actively abusing alcohol were excluded, as well as samples from subjects who had received carbamazepine, phenytoin or phenobarbital (n = 36), steroids (n = 4), l-thyroxine (n = 30), thiazide diuretics (n = 7), oral contraceptives (n = 2) or statin-class medications (n = 2) within two weeks of blood sampling. Some samples were excluded based on multiple exclusion criteria.

The final cohort therefore comprised 174 subjects, including 62 white males, 33 black males, 50 white females, 28 black females and one Asian American female. The mean age of the cohort was 42.5 years (SD 13.6 range 18–76). Twenty-six met DSM-IIIR criteria for Bipolar Disorder, mixed and 148 for Bipolar Disorder, manic. Using the ROC criteria, 40 were categorized as mixed subtype and 134 as pure subtype.

The mean serum cholesterol levels of the mixed manic subtype (165.5 mg/dl SD 34.7) and the pure manic subtype (182.5 mg/dl SD 41.2) were significantly different using the ROC definition of mixed mania ($F = 6.437$, $p = 0.012$, Table 1). Likewise cholesterol levels increased with advancing age ($F = 14.505$, $p < 0.001$, Table 1). The mean cholesterol levels of males (176.2 mg/dl SD 41.1) and females (182.5 mg/dl SD 39.6) were not significantly different ($F = 0.008$, Table 1). Body mass index (BMI) was available for 164 (94 %) of the these subjects. Mean BMI

Table 1 ANOVA comparing cholesterol levels by manic subtype (mixed vs. pure) and sex, with age as a covariate. Mean cholesterol level by age category are listed

	Cholesterol Levels	F	p
Sex			
Male (n = 95)	176.2 mg/dl (SD 41.1)	0.008	ns
Female (n = 79)	181.5 mg/dl (SD 39.6)		
ROC Manic Subtype			
Mixed (n = 40)	165.5 mg/dl (SD 34.7)	6.437	0.012
Pure (n = 134)	182.5 mg/dl (SD 41.2)		
Sex x Subtype		0.704	ns
Age			
< 30 years	140.5 mg/dl (SD 34.1)	14.505	< 0.001
30–39 years	177.5 mg/dl (SD 30.9)		
40–49 years	177.2 mg/dl (SD 44.9)		
50–59 years	194.9 mg/dl (SD 43.3)		
≥60 years	193.7 mg/dl (SD 36.5)		

for subjects meeting the ROC mixed mania criteria (26.7 SD 6.6 n = 38) and for subjects meeting the ROC pure mania criteria (27.2 SD 6.6 n = 126) did not differ (t = –0.457, df = 162). When the DSM-IIIR definition for Bipolar Disorder, manic and mixed, were applied cholesterol levels were not different between the episode subtypes (F = 2.673, ns).

The percentile assignments of cholesterol levels differed from those expected from national norms in both the ROC-defined pure manic subtype ($\chi^2 = 54.224$, df = 8, $p < 0.001$), the ROC-mixed manic subtype ($\chi^2 = 90.750$, df = 8, $p < 0.001$), and the combined group ($\chi^2 = 115.4$, df = 8, $p < 0.001$, Table 2). Inspection of percentile group distribution of all manic subjects in Fig. 1 suggests a natural separation of the sample at the 10th percentile, with a greater than expected number of subjects falling into the lowest decile. Nineteen of 40 (47.5 %) subjects with mixed manic symptomatology have cholesterol levels in the lowest 10th percentile, in contrast to 36 (26.9 %) of 134 with pure manic symptomatology ($\chi^2 = 6.067$, df = 1, p = 0.014). Likewise, 19 of 55 (34.5 %) subjects in the lowest decile have mixed symptomatology, in contrast to only 21 of 119 (17.6 %) subjects in the upper percentiles ($\chi^2 = 6.067$, df = 1, p = 0.014).

Discussion

In the current report cholesterol levels increase with advancing age, consistent with population norms. Cholesterol levels were not different between males and females, but were lower in mixed manic compared to the pure manic subjects. Cholesterol levels in both subtypes were lower when compared with population norms in

Table 2 Percentile distribution of cholesterol levels by mixed and pure subtypes, the total group and expected distribution for the total group

Percentile	ROC Mixed Manic	ROC Pure Manic	Total	Total Expected
< 5th	14	20	34	8.7
< 10th, ≥ 5th	5	16	21	8.7
< 15th, ≥ 10th	4	8	12	8.7
< 25th, ≥ 15th	5	17	22	17.4
< 50th, ≥ 25th	6	32	38	43.5
< 75th, ≥ 50th	3	28	31	43.5
< 85th, ≥ 75th	2	6	8	17.4
< 90th, ≥ 85th	1	2	3	8.7
< 95th, ≥ 90th	0	2	2	8.7
≥ 95th	0	3	3	8.7
Total	40	134	174	174

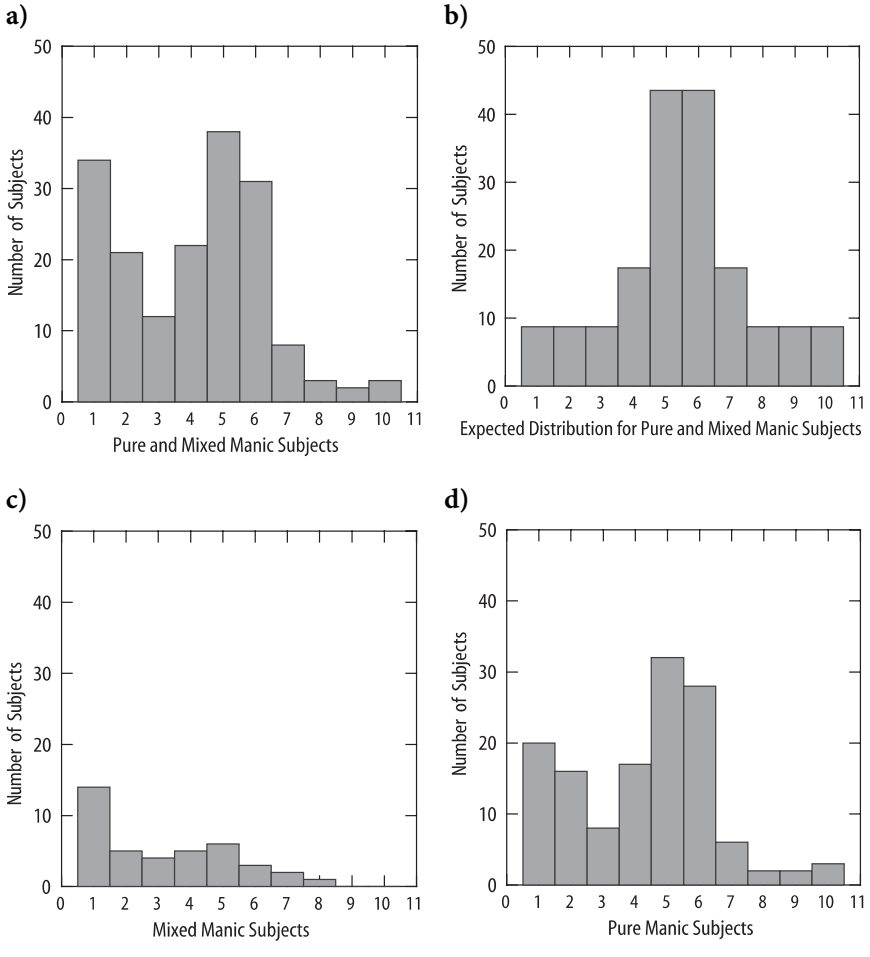

Fig. 1 Cholesterol percentile group distribution for all subjects and the expected distribution for all subjects, and the group distribution by mixed and pure manic subtypes

keeping with one previous report, and this was especially prominent in the mixed manic subtype. When compared with national norms, an excess number of subjects had cholesterol levels in the lowest decile than was expected. An association of these subjects and the mixed manic subtype was also noted.

The underlying mechanism for lower cholesterol levels during manic states is unclear. The particularly low levels of cholesterol in subjects during mixed episodes tend to follow the observation of lower cholesterol levels in subjects during major depressive episodes. Possible explanations for this finding are similar to those proposed for hypocholesterolemia during depressive episodes. These include differences in nutritional status and state-dependent immune activation.

Although decreased appetite may lead to poor nutrition and hypocholesterolemia in depression, depressive episodes tend to be more insidious than manic episodes. Frequently there is greater treatment delay during which symptoms, such as decreased appetite with resulting poor nutrition, may develop. In contrast, patients in manic episodes come sooner to treatment. Winokur (1976) reported that 66% of patients hospitalized for treatment of mania will be admitted within 4 weeks of its development, a shorter duration than would typically be required to affect nutritional status and cholesterol levels. It is also unclear whether changes in appetite and nutrition are specific to either manic subtype (Cassidy et al. 2000). The recency of depressed episodes in this cohort is not known. Therefore the possibility that depression may have closely preceded a greater portion of mixed than pure manic states must be considered. BMI was not different between the two groups, however, suggesting that weight loss was a less likely explanation for the observed hypocholesterolemia.

Cholesterol may be a negative acute phase reactant (Ettinger and Harris 1993). Acute decreases in cholesterol levels occur in response to IV administration of pro-inflammatory cytokines such as IL-1β (Hermus et al. 1992), IL-2 (Wilson et al. 1989) and TNF-α (Ettinger et al. 1992). Elevations in soluble interleukins–2 and –6 receptors (Maes et al. 1995) and positive acute phase proteins (Maes et al. 1997) during manic episodes have been reported, similar to what has been observed during depression (Maes 1993, Kronfol and Remick 2000). Differences during mixed and pure manic states have received less attention. Recently we reported hypoalbuminemia and leukocytosis in subjects during mixed mania compared with subjects during pure mania and proposed heightened immune activation as a possible mechanism (Cassidy et al. 2002).

Pharmacological treatment of hypercholesterolemia may be associated with depressive symptoms possibly as a result of alterations in membrane fluidity which may affect brain serotonin function (Engelberg 1992). Lowering cholesterol levels may reduce serotonin neuronal activity by increased presynaptic reuptake and decreased postsynaptic receptor number or function (Hawton et al. 1993, pp 823–824). Lowering cholesterol levels, for example, through immune activation, may functionally decrease serotonin and lead to depressive symptoms.

Although this study is not a direct comparison of depressive episodes with pure and mixed manic episodes, our finding of lower cholesterol levels during mixed manic episodes is consistent with observations during depressive episodes. This finding adds to the growing evidence of pervasive biological similarities between mixed mania and depression, apart from common symptomatology such as depressed mood and suicidality. Although the exact relationship between mixed mania and depression is unclear, the current finding supports viewing mixed states as a specific subtype distinct from pure mania, and demonstrates another biological similarity between depression and mixed mania.

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