CLINICAL FEATURES

Circadian Phenotype in Patients with the Co-Morbid Alcohol Use and Bipolar Disorders

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Abstract — Aims: Alcohol misuse is associated with bipolar disorder. Abnormalities in the circadian clockwork play a role in the pathogenesis of bipolar disorder. Alcohol intake is likely to affect the circadian phenotype. We aimed at analysing the behavioural trait of the preference to morning or evening hours for the daily activities in bipolar disorder patients with or without the co-morbid alcohol use.

Methods: Our nationwide sample of families included patients with bipolar disorder born during 1940–1969 having at least one hospitalization due to bipolar disorder during 1969–1991 and their first-degree relatives. All the 148 participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders and assessed using the Morningness–Eveningness Questionnaire whose factor matrix applying for the maximum likelihood principle was calculated for the first time.

Results: Patients with the co-morbid alcohol use disorder were more of the morning type as compared with patients with bipolar disorder only.

Conclusions: Co-morbid patients preferred more the morning hours for their daily activities, indicative of alcohol consumption having an effect on the circadian clock.

INTRODUCTION

Abnormalities in circadian rhythms may constitute a key component in the pathogenesis of bipolar disorder in particular, or affective disorders in general (Bunney and Bunney, 2000; Mansour et al., 2005a). Individuals place themselves on a continuum from morningness to eveningness (early birds to night owls) as a function of time of the day they routinely feel the best and refer to the preferred time of day for their daily activities (Kerkhof, 1985; Taillard et al., 1999; 2004). Evening types are predisposed to anxiety (Broman and Hetta, 1998), depression (Drennan et al., 1991; Broman and Hetta, 1998; Chelminski et al., 1999; Taillard et al., 2001; Murray et al., 2003) and initial insomnia (Broman and Hetta, 1998), whereas morning types spend time awake longer and have a lowered quality of sleep (Carrier et al., 1997; Taillard et al., 1999). Data are conflicting though (Gale and Martyn, 1998).

The behavioural trait of morningness to eveningness seems to reflect the phase position of the circadian rhythms and correlate with the circadian period (Kerkhof and Van Dongen, 1996; Duffy et al., 2001). There is a difference in the phase positions of core temperature rhythm and sleep between the morning and evening types (Estroff et al., 1985; Kerkhof and Van Dongen, 1996; Duffy et al., 1999). This explains why manic episodes of bipolar disorder may be triggered by disruption in the sleep–wake cycle (Wehr et al., 1987), whereas sleep deprivation tends to alleviate depression in patients with bipolar disorder (Colombo et al., 2000).

Lithium is commonly used to treat bipolar disorder. In experiments with cultured cells, GSK3-beta phosphorylates and stabilizes the orphan nuclear receptor NR1D1, a negative component of the circadian pacemaker. Treatment of cells with lithium inhibits glycogen synthase kinase 3-beta, leading to degradation of NR1D1 and activation of the Arntl gene, a positive component of the circadian pacemaker (Yin et al., 2006). Lithium acts directly on the circadian pacemaker cells and lengthens the period of circadian rhythms (Reghunandan et al., 1989; Khalsa et al., 1993; Abe et al., 2000; Padiath et al., 2004).

Since data on the circadian phenotype of patients with bipolar disorder are still scarce, we aimed at analysing the preference to the morning or evening hours in individuals with or without the co-morbid alcohol use disorder to provide information about their circadian-type preference.

METHODS

Subjects

The search for participants began with the nationwide Hospital Discharge Register of Finland, which was used to identify all patients who were hospitalized due to bipolar disorder (proband) in 1969–1991 inclusive (ICD-8 codes 296.10 or 296.30 before the year 1987, or DSM-III-R codes 296.4, 296.5 or 296.6 during 1987–1991). Data on relatives were gathered from the nationwide Population Register and linked back to the records of the hospital discharge register in order to track the first-degree relatives of those born in 1940–1969 inclusive and to construct pedigrees. All available medical records of the whole family (siblings and parents) were collected. On the basis of these records and blinded to each other, specialists in psychiatry assessed the primary diagnosis plus co-morbid conditions according to the DSM-IV criteria. Diagnoses were discussed for consensus, and no disagreement remained after this procedure. Probands were contacted through their physician in charge, and if the proband gave permission other family members were contacted. All those who gave their informed consent were interviewed using the SCID-I (Structured Clinical Interview for DSM-IV Axis I Disorders). Finally, the study sample included 148 individuals, of whom 47 (11 with and 36 without the co-morbid alcohol use disorder) had bipolar

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disorder, 26 had alcohol use disorder, 30 had mental disorder exclusive of bipolar or alcohol use disorders and 56 had no diagnosis.

Self-report
The Morningness–Eveningness Questionnaire (MEQ) includes 19 items estimating the preference for the timing of different activities and behaviours (Horne and Östberg, 1976). The sum of these 19 items yields the Morningness–Eveningness Score (MES), ranging from 16 to 86. Considering the daily activities (behavioural traits), the highest scores indicate a definite preference to the morning hours (morningness) and the lowest a definite preference to the evening hours (eveningness).

Ethics
The Ministry of Social Affairs and Health and the Ethics Committee of the National Public Health Institute approved the study. After complete description of the study to all subjects, they signed the written informed consent for participation.

Statistics
Concerning the MEQ, the sum score may override components of the morning- and evening-based traits being distinct from one another. In order to analyse, whether any component of significance was to contribute to the MES, a factor matrix according the maximum likelihood principle and employing the algorithm by Jöreskog (1977) was produced for analysis of the MEQ. In order to observe, whether there were any association between the circadian preference and affection status, partial correlation coefficients were calculated and controlled for age (in years), sex (male or female), education (in years), psychotropic medication (yes or no), smoking (yes or no) and body mass index in each analysis. In order to judge, whether the affection status was an independent predictor of the circadian preference, the MES or the score on a factor of the MEQ was the dependent variable in the linear regression models. Age (in years), sex (male or female), education (in years), psychotropic medication (yes or no), smoking (yes or no), body mass index and affection status (bipolar disorder with or without co-morbid alcohol use disorder) were the covariates in each model. Post hoc comparisons were calculated in order to find out between-group differences (bipolar disorder with or without co-morbid alcohol use disorder designated as Groups 1 and 2, respectively). Statistical analyses were performed using the SSPS 13.0 and Survo MM software.

RESULTS

Factor analysis
The factor analysis yielded four factors (see Table 1). The reliability for the unweighted sum of all items, considering the factor images and scores, was good (Cronbach's alpha = 0.82). The factor F1 contains six items (general preferences), F2 eight items (morning activities), F3 four items (evening activities) and F4 one item (times for physical work).

In subsequent linear regression models, separate for each factor, the $R^2$ values explaining the variance of the MES were 0.713, 0.557, 0.357 and 0.432 for the first to the fourth factor, respectively.

Correlation coefficients
Since four factors emerged from the factor analysis, correlation coefficients were calculated for the MES and each factor, and for the affection status of interest (bipolar or alcohol use disorder, or both as co-morbid). Whereas bipolar or alcohol use disorder did not correlate significantly with the circadian phenotype, the co-morbid disorder was associated with the factor F2 ($r = 0.52, P = 0.04$; see Table 2).
DISCUSSION

For our work we carried out a retrospective lifetime diagnostic assessment together with a self-report of behavioural trait. Both correlation computations and regression models indicated that patients having the co-morbid bipolar and alcohol use disorders displayed the circadian preference in direction to the morning hours. Post hoc comparisons indicated further that scores on two factors were on average antithetical (positive versus negative) in Group 1 and Group 2, respectively, suggesting traits towards the preference to the morning hours among those with co-morbid alcohol use disorder. In addition, comparing bipolar disorder patients with the subjects of no diagnosis yielded a difference in two factors, suggesting more the preference of evening hours (six items) instead of morning hours (one item) in bipolar patients.

Our findings agree with a study in which the circadian-type preference for evening activities has been shown in bipolar type 1 disorder (Mansour et al., 2005b). On the other hand, they are in contrast to the results from our previous study in which seasonal variations were associated with bipolar disorder whereas the circadian-type preference was not (Hakkakainen et al., 2003). However, the samples of participants were different between the present and earlier studies (bipolar families and bipolar twins, respectively), which probably explain this conflict.

Our key finding herein is that the co-morbid alcohol use disorder makes a difference in the circadian preference. For explanation, there are at least two possibilities. First, the circadian preferences have been different before the onset of illness, the co-morbid patients having more preference to the morning activities and probably a shorter circadian period. Second, the circadian preferences have been similar but changed in the course of illness because of alcohol use or other reasons that are not characterized yet. Our cross-sectional design does not allow causative deductions. However, we suggest that a prolonged alcohol misuse, leading to a lifetime diagnosis of alcohol abuse or alcohol dependence, may result in the situation in which the circadian preference has changed from the evening to morning type in individuals with bipolar disorder. This hypothesis needs testing in subsequent studies.

A limitation is that we assessed the circadian preference with a self-report and did not measure actual indicators of the circadian rhythms. However, we present herein for the first time a factor matrix of the MEQ and point out a significant association of the co-morbid alcohol use disorder with the score on the eight items of morning activities.

The self-report instrument used in our study, i.e., the Horne and Östberg MEQ, has been evaluated as a fair predictor of the endogenous circadian period and phase (Sack et al., 2007). In addition, laboratory studies applying for constant routine protocols have demonstrated that the phases of circadian melatonin and temperature rhythms are related to the self-reported circadian preference (Duffy et al., 1999; Griefahn, 2002). It is possible or even plausible that alcohol misuse induced the change in the circadian preference from evening to morning hours in our study, thereby indicating a link of abnormalities in

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**Table 3. Background, circadian preference and levels of functioning in bipolar disorder with (Group 1) or without (Group 2) the co-morbid alcohol use disorder**

<table>
<thead>
<tr>
<th>Group 1 (n = 11)</th>
<th>Group 2 (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age</td>
<td>49.38</td>
</tr>
<tr>
<td>Education</td>
<td>11.75</td>
</tr>
<tr>
<td>BMI</td>
<td>27.07</td>
</tr>
<tr>
<td>MES</td>
<td>54.22</td>
</tr>
<tr>
<td>Factor 1</td>
<td>1.00</td>
</tr>
<tr>
<td>Factor 2</td>
<td>0.22</td>
</tr>
<tr>
<td>Factor 3</td>
<td>0.13</td>
</tr>
<tr>
<td>Factor 4</td>
<td>0.11</td>
</tr>
<tr>
<td>GAF2</td>
<td>58.57</td>
</tr>
<tr>
<td>MES</td>
<td>54.22</td>
</tr>
</tbody>
</table>

CI = confidence interval; SD = standard deviation; BMI = body mass index; MES = Morningness–Eveningness Score; GAF1 = global assessment of functioning, current; GAF2 = global assessment of functioning, highest past year.

**Table 4. Regression analysis of the circadian phenotype**

<table>
<thead>
<tr>
<th></th>
<th>Beta</th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.37</td>
<td>1.70</td>
<td>0.1</td>
</tr>
<tr>
<td>Sex</td>
<td>−0.43</td>
<td>−1.72</td>
<td>0.1</td>
</tr>
<tr>
<td>Education</td>
<td>−0.17</td>
<td>−0.77</td>
<td>0.5</td>
</tr>
<tr>
<td>Psychotropic medication</td>
<td>0.09</td>
<td>0.40</td>
<td>0.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>−0.16</td>
<td>−0.64</td>
<td>0.5</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.19</td>
<td>0.84</td>
<td>0.4</td>
</tr>
<tr>
<td>Co-morbid disorder</td>
<td>0.65</td>
<td>2.26</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Adjusted R^2 = 0.09 for the model of Factor 2 as the dependent variable.

*Standardized coefficients.
the circadian clockwork induced by alcohol misuse to shorter circadian periods or advanced circadian phase positions.

Our results herein show that patients with bipolar disorder having co-morbid alcohol use disorder are prone to have a circadian phenotype of the morning type as compared with those having bipolar disorder only. Earlier studies have pointed out that alcohol misuse is associated with bipolar disorder. Patients with alcohol dependence have a greater prevalence of bipolar disorders than the general population, and patients with bipolar disorder have increased rates of alcohol use disorders (Freed, 1969; Mendlewicz et al., 1972; Morrison, 1974; Dunner et al., 1979; Estroff et al., 1985; Regier et al., 1990).

This high prevalence of co-morbid substance use disorders in bipolar disorder suggests that this kind of co-morbid condition may be an intrinsic component of bipolar disorders (Schulze et al., 2006). Moreover, alcohol consumption has an effect on the human physiology that is dependent on the circadian time (see the review by Danel and Touitou (2004)). For example, craving for the first drink of the day occurs most often in the mid-morning (Danel et al., 2003).

Repeated alcohol intake influences the circadian rhythm of core body temperature and results in hypothermic and hyperthermic effects during the day and night, respectively (Danel et al., 2001). In rats, chronic ethanol intake reduces the responsiveness of the circadian system to acute stimulation with light exposure (Rosenwasser et al., 2005), which agrees with the findings of the vulnerability of the circadian pacemaker to chronic alcohol administration (Chen et al., 2004).

Alcohol use enhances the serum testosterone levels (Danel et al., 2006) and disrupts the secretion of melatonin (Danel and Touitou, 2004). But, there are contradictory findings as well that challenge the desynchronization of the circadian rhythms as a plausible mechanism of action for alcohol consumption on the circadian clockwork (Danel and Touitou, 2006). Links between the circadian system, alcohol consumption and bipolar disorder are highlighted on the basis of genetic studies. Administration of ethanol to rats for a period of 2 weeks disrupts the expression of the rPer2 gene in the arcuate and suprachiasmatic nuclei, suggesting the effect on the circadian pacemaker (Chen et al., 2004). In addition, mPer2 (Brdm1) mutant mice whose circadian period is shortened display lower expression levels of the glutamate transporter EaAT1 gene and increases in extracellular levels of glutamate and normalizes the increased ethanol intake in these mice.

Recently, the D site of albumin promoter (albumin D-box)-binding protein has been identified as a candidate gene for bipolar disorder and alcohol dependence (Niculescu et al., 2000), and the stress reactive genetic animal model of bipolar disorder and co-morbid alcoholism has been reported (Le-Niculescu et al., 2008). Another recent study reveals that there are manic-like behaviours in Clock mutant mice and that some of these behaviours can be reversed with lithium treatment (Roybal et al., 2007). In addition to these animal studies, variants in the Per2 gene have been associated with alcohol consumption in humans (see the review by Spanagel et al. (2005b)). Altogether, further studies of both phenotype and genotype are important to elucidate clinically relevant and tailored treatment interventions.

In conclusion, patients having the co-morbid alcohol use and bipolar disorders have more often the circadian phenotype of the morning type as compared with those with bipolar disorder only.

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REFERENCES


