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Familiality and clinical outcomes of sleep disturbances in major depressive and bipolar disorders

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ABSTRACT

Objective: Sleep disturbances are frequently observed in major depressive (MDD) and bipolar disorder (BD). This study reported sleep profiles of patients and their relatives versus controls, and examined the familiality of sleep features in mood disorder families. We also evaluated the influences of sleep disturbance on patients' quality of life (QOL), functional impairment, and suicidality.

Methods: We recruited 363 BD and 157 MDD patients, 521 first-degree relatives, and 235 healthy controls, which completed a diagnostic interview, Pittsburgh Sleep Quality Index (PSQI), and QOL questionnaire. The magnitude of heritability of sleep features was calculated and familiality was evaluated by mixed regression models and intraclass correlation coefficient (ICC). The associations between sleep problems and clinical outcomes were examined using multiple regression models.

Results: More than three-quarters of mildly-ill patients were classified as "poor sleepers". MDD patients had significantly worse sleep quality as compared to BD patients. Moderate but significant familial aggregation was observed in subjective sleep quality, sleep latency, disturbance, daytime dysfunction, and global score (ICC = 0.10–0.21, $P < .05$). Significant heritability was found in sleep quality (0.45, $P < .001$) and sleep disturbance (0.23, $P < .001$). Patients with good sleep quality had better QOL and less functional impairment ($P < .05$) than poor sleepers. Poor sleep quality and nightmares further increased the risk for suicidal ideation ($OR_{adj} = 2.8$) and suicide attempts ($OR_{adj} = 1.9–2.8$).

Conclusion: Subjectively measured sleep features demonstrated significant familiality. Poor sleep quality further impaired patients' daily function and QOL, in addition to increasing the risk of suicidality, and thus requires special attention in related clinical settings.

Introduction

Previous studies have shown a link between sleep disturbances and emotional dysregulation [1,2]. Sleep complaints are commonly observed prodrome symptoms of affective disorders [3]. The current DSM-IV diagnostic system for mood disorders lists sleep complaints as one of the major symptoms in both manic and depressive episodes. Patients usually have a reduced need for sleep during manic episodes, whereas patients in the midst of a depressive episode exhibit either insomnia or hypersomnia. Even in a remission period, a high percentage of patients with mood disorders continue to encounter sleep problems [4]. For instance, up to 70% of euthymic bipolar patients showed clinically significant sleep disturbances [5]. In addition, insomnia during a remission period is associated with a substantially increased risk for the recurrence of a depressive episode [6]. Moreover, in the general population, non-depressed individuals who suffer from insomnia also have a twofold risk of developing depression during follow-up [7]. Overall, sleep disturbances are not only present before and at the time of making a diagnosis, but they are also among the most common residual symptoms that occur during remission periods [8]. However, relatively few studies exist that examine detailed features of sleep problems in patients with mood disorders [9]. To what extent different sleep features are present in BD versus MDD patient groups is less clear at this time.

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Family, twin, and adoption studies have found evidence of strong familial aggregation in mood disorders. In addition to the diagnosis of mood disorders, several clinical features also run in families, such as substance abuse, personality, history of suicide attempts, and the level of social functioning [10,11]. Although sleep disorders have been reported to exhibit familial aggregation [12] and the risk of familiality was further increased in patients with an earlier age of onset (<40 years) of insomnia [13], very few studies have examined the familial aggregation of subjectively measured sleep related phenotypes [14]. Substantial familiality of sleep disturbances in mood disorder families would indicate its potential to serve as an endophenotype for further genetic analysis [15]. In general, subjective assessment of sleep quality is more feasible in studies with a larger sample size and is often applied in clinical and epidemiological studies with good validity. One commonly used sleep questionnaire is the Pittsburgh Sleep Quality Index (PSQI), which assesses multiple components of sleep quality, including both numbers and severity of sleep problems in different dimensions, such as sleep duration and efficiency [16]. The current study aimed to examine the aggregation and heritability of sleep features in families of mood disorders using a standard subjective measurement, the PSQI. We also evaluated whether or not specific characteristics of sleep disturbances have a higher magnitude of familiality than others. In particular, the liability of sleep problems in different diagnostic groups of mood disorders might vary.

Finally, patients with mood disorders often exhibit difficulties with social settings, interpersonal relationships, and occupational functioning [17]. The phenomena of persistent sleep disturbances are not only related to chronic illness courses with more recurrent manic and depressive episodes, but are also related to poor quality of life (QOL) and even suicidality [14,18]. Previous studies have reported that BD patients with sleep problems showed more impaired QOL, particularly in the physical and psychological domains [19], as well as impaired global function than those without sleep complaints [20]. Gruber and colleagues [21] measured total sleep time among patients and found that short (<6 h) and long (≧9 h) sleepers have more severe mania and depressive symptoms, poorer life functioning, and QOL as compared to normal sleepers. Moreover, frequent insomnia and nightmares are related to increased severity of clinical symptoms [22], worse treatment response [23], and increased risk of suicidal ideation and suicide attempts in MDD patients [24]. Using a standardized measure such as PSQI, we evaluated the relationships between different sleep quality and quantity variables and QOL, functional impairment, and suicidal behaviors in patients with mood disorders.

The current study examined whether patients with BD and MDD exhibit different sleep problems and to what extent their relatives have sleep complaints, and compared with healthy controls. We also investigated the magnitude of familial aggregation for different sleep components in mood disorder families among the two diagnostic groups. Finally, among patients with mood disorders, we hypothesize that those who do not sleep well (poor sleepers) have worse QOL, more functional impairment, and increased risk of suicidality than good sleepers.

Methods

Research design and subject recruitment

We conducted a family study of mood disorders in Taiwan. Patients aged between 18 and 70 years who were diagnosed with MDD, BD-I (bipolar disorder I) or BD-II (bipolar disorder II) based on the DSM-IV criteria were eligible for enrollment. The clinical global impression — severity scale (CGI-S) was assessed by psychiatrists in six central and regional hospitals to measure symptom severity. Patients who were at most mildly ill (i.e. CGI-S ≦3) were consecutively referred by psychiatrists from 2008 to 2011 as index probands. The mean CGI-S scores in BD patients were not significantly different from those in MDD patients ($P = .32$). Patients who were diagnosed with schizophrenia, schizoaffective, or substance-induced mood disorders were excluded. Patients whose diagnoses were changed during the data collection period were also excluded.

We intended to recruit all available family members with whom the probands provided permission to contact. The majority of participating family members were biological first-degree relatives (i.e. father, mother, siblings and adult offspring, total N = 618, 95.32%). Only first-degree relatives were considered in the following analysis. Healthy controls were recruited from the community by sending leaflets or word-of-mouth, and these subjects were then screened for mood disturbances and other major psychiatric disorders using the Composite International Diagnostic Interview (CIDI). Due to the relatively high prevalence of mood disorders in the general population, we recruited controls aged between 35 (approximately the mean onset age of mood disorders) and 70 years to reduce the likelihood of having control subjects develop mood disorders after recruitment. The study was approved by the institutional review board of all concerned institutions and hospitals. All participants provided written informed consent after the study procedures had been fully explained to them. In total, we recruited 1275 participants, including 657 probands (318 BD-I, 150 BD-II, and 189 MDD), and 618 first-degree relatives (141 fathers, 206 mothers, 197 siblings, and 74 adult offspring). In addition, 235 healthy controls were recruited in the present study.

Diagnostic and phenotypic assessment

Composite International Diagnostic Interview, CIDI

All participants were interviewed with the Chinese version of the WHO Mental Health 2000 version of the CIDI [25]. The CIDI is a comprehensive, fully-structured interview for the assessment of mental disorders. The CIDI has been used extensively in many large-scale epidemiological surveys and cross-cultural studies demonstrating good reliability and validity [26]. We used the CIDI interview to conform to clinical diagnosis and to derive diagnostic information for the relatives of index probands. If there was any inconsistency between the CIDI and clinical diagnosis in the index probands, further consultations with psychiatrists were made and patients were re-interviewed to gather additional information and to reduce the chance of misdiagnosis. Using the CIDI interview, we retrospectively collected demographic variables (e.g. socioeconomic status, lifetime symptoms and clinical features of mood disorders, and information on suicidal ideation and attempts).

Sheehan Disability Scale, SDS

Functional impairment was assessed by the Sheehan Disability Scale, SDS. The SDS asks respondents to what extent on a 0 to 10 scale their functions at home, at work, in their social life, and in relationships were impaired by a depressive or manic episode in the last year. The most severe score across all four domains was then coded as the overall role impairment, which was adopted in Liao et al. [27]. Higher scores mean greater disability (0: no interference; 1–3: minor interference; 4–6: moderate interference; 7–9: severe interference; 10: very serious interference).

Pittsburgh Sleep Quality Index, PSQI

The PSQI is a self-reported questionnaire to evaluate quantitative and qualitative sleep quality during the previous 1 month of data collection [16]. It has been widely used in clinical and epidemiological studies. The PSQI consists of seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global PSQI score is obtained by summing up scores from the seven components (ranged 0–21). Higher scores represent poorer sleep quality. A